

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

**Palliative care – filling a gap in the CUO diagnostic pathway?
Carol Davis**

Cast your minds back, if you can, to about four years ago. I can't remember it very well but I do remember there was a funny day, and on that funny day I did an educational supervision with one of our SPR's, one of our trainees, under a tree in the hospice garden, everyone's idea of what a hospice is like I am sure, and we decided to do a Hot Case review and we picked a patient that we had both seen in the hospital in the last two days on two separate instances. This was a female, middle aged, extremely young **morris**, a female physics teacher with a new diagnosis of confirmed CUP. We both remembered her saying things like: 'it's like standing up in front of a class and not knowing what to say'. This woman was completely floored by having a carcinoma of unknown primary. This led on to Lucy and I discussing that case, and me not being half as nice as people think that I am, being in palliative care, I sent her away with a very strict deadline to go and do a literature search and come back to me in three weeks time, which she did. We found no literature on the sort of things that we were interested in, so we went on to define a research question and design a research study.

The pilot study mixed methods, largely, but not totally, qualitative and the aims were:

- to explore the patient's understanding of cancer of unknown primary,
- how they describe it,
- how they rationalise the unknown nature of the primary,
- to identify any concerns they might have,
- to assess their quality of life, and
- to analyse this in conjunction with themes emerging from the interview.

The patients were recruited from two acute hospital NHS trusts, either as inpatients or outpatients. The inclusion criteria were fairly pragmatic. They needed to be aware of their diagnosis of Cancer of Unknown Primary, they needed to be able, and willing, to provide written, informed consent and well enough to talk to the researcher. From the outset we planned purposive sampling, so we wanted to get some people who, I now realise, were the provisional CUP patients, some patients who were confirmed CUP patients, and some patients from the diagnosis of CUP with a possible identifiable primary. Patients were seen in their own home, or in the hospital setting, over a year. They underwent semi structured interviews, lasting around about 30 minutes, which were taped and then independently transcribed. The themes coming from each interview were discussed in an anonymised way with the next interviewee, so that you are constantly checking by saying things like 'somebody said..... do you ever feel like that?' or things like that.

We chose the McGill Quality of Life Questionnaire, some of you may be familiar with it, and others may not. I don't tend to dwell on that data at all today but we chose that particular quality of life questionnaire because it had an existential domain with things like the 'Why me' type questions in it and it also had the domain assessing how well supported, or not, people felt.

I don't really want to go through the slides in any details, but really just to show people who are not used to reading or taking part in qualitative research that there is a rigour to it, just as there is for quantitative research. So I don't plan to talk through this in great detail but I would like to say that the themes that were emerging and the themes that we ended up with at the end of the recruitment period were compared with the demographic and the quality of life data, and in particular we were very interested in length of time from diagnosis, performance status and disease extent and whether that shaped in any way people's perceptions of what was going on for them.

Over that year period we only identified sixteen patients and five of those deteriorated rapidly before seeing i.e. within a day or two. Those happened, perhaps not surprisingly, to be people who were not having, or who were not planned to have, active anti-cancer treatment. As things

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turned out our purposive sampling for that group went by the way and the patients that we did recruit actually all had confirmed CUP. One patient declined and ten patients were recruited. You will see that the median age was young – 60.5 years. There was quite a range and the median and mean were certainly brought down by the 23 year old patient. That is a young population for CUP and we need to interpret the results bearing that in mind.

Nine of the patients had CUP of entirely unknown origin and one had a CUP of possible ovarian origin. The time from diagnosis varied from 2 – 15 months and the median was 3. Seven were having, or had had, chemotherapy. One had had one fraction of palliative radiotherapy for bone pain and two of the patients having chemotherapy had also had some palliative radiotherapy. Only one and had no anti-cancer treatments. All had specialist palliative involvement. Eight interviews were in the patients home and two were in hospital. Three patients chose to have their partners present at the interview. We made it clear that their views wouldn't be included in the analysis. It transpired through one of the interviews, that the patient was actually quite confused and the data was not included.

So, we got some themes:

- The first theme was uncertainty contrasting with stoical expectance.

'I think that if that one there is a secondary and it can cause you that much jip if there is a primary it could do you double the damage. I just don't understand how it can hide away somewhere. It is the not knowing that is the horrible thing, the uncertainty of it all. If I knew I would be more at ease'.

Many patients struggled with the uncertainty, indeed most of them. Some described it as 'an ominous sense', that the cancer, that they did not know where it had come from, was spreading, was lurking, was floating. *'It's confusion because you don't know what to expect. I know there are loads and loads of cancers around and they know where most of them are. Why am I so different? Why are these unknown primaries? So I feel like screaming sometimes, literally screaming. If they said where they are for me it would be peace of mind.'*

One participant contrasted the certainty of his diagnosis of leukaemia twenty years previously with the uncertainty of an unknown primary. *'Got no feeling where the actual cancer is and my wife quite often will prod me to see if she can find it. With the cancer I had before I knew exactly where it came from but not knowing with this cancer makes me feel unaware. Now I would like to know where it is coming from'.*

On the other hand a few patients said that they accepted the situation. They accepted that their cancer, and where it had come from, was unknown and they did not think about this because there were was no point. *'If it is there it's there. I mean it doesn't make any difference to me now so trying to think about it is to me a bit of a waste of time'.*

The patient with possible ovarian primary cancer had made a conscious decision to believe it was ovarian cancer and that the targeted chemotherapy would be effective. *'As far as I'm concerned it is in my ovaries. Because I am being treated for ovarian cancer I am not looking for anything else at the moment. It would be much more difficult if I did not know where it was'.*

Interestingly, out of our ten patients, she was the second patient with a second primary. She had been treated for breast cancer seventeen years previously and she contrasted very much the difference between being treated for breast cancer and for CUP.

- The second theme is their understanding of CUP and for the causality of it.

All patients who had an entirely unknown primary – nine out of ten – discussed being told

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that they had cancer, but that the primary site could not be found. Some said they did not fully understand this, only that they had cancer that could not be cured. *'This kind of nonspecific ... kind of ... they have not found the primary tumour, but it is spreading all over the place'*.

Others used graphic descriptions: *'I know that I have this alien under my arm, apart from that I don't know where the rest are'*.

Several patients had searched for possible causes, attributing it to past injuries, smoking, stress, or couldn't think of a possible cause. Some thought that the cancer may have been present for a very long time and may have suddenly popped up at a later date. One patient very vividly and vocally, described it as being like shingles.

- The third theme concerned undergoing multiple investigations, something that has been touched on several times during the morning. It won't surprise you that all the participants with an entirely unknown primary raised the theme of the number of investigations they had undergone to no avail to search for the primary site. *'A whole series of tests, CT scans, MRI, you name it, I had it, and in the end they said, 'Well we can't trace it'. They seem to have covered my whole body with things'*.

Two patients described how they underwent multiple investigations and were then suddenly summoned to be told the bad news, or to be treated with enormous urgency. *'Then it was wham - bam - buff you have got all these cancers, and we don't know where they are coming from.'*

- The fourth theme was being unable to treat CUP .

Another universal theme was the inability to effectively treat a cancer if the primary site is truly unknown. Many patients spoke of being able to target treatment much more effectively if you knew where it was. *'If they knew where it was then they would be doing something about it. I mean they have told me they cannot do anything about it at all. It is only palliative and I can't accept that'*.

Patients mentioned the difficulty in predicting response to treatment and whether some ambivalence about whether undergoing treatment would be worthwhile. One patient described the need for a second opinion to achieve closure. Two patients referred to the difficulties of having untried and untested treatment. *'She said they hadn't done that mixture before, so the side effects might cancel each other out, or it might make it worse, so they're not really sure. They are not sure about the long-term side effects and they have got to give me a very high dosage'*.

This contrasts with a patient with a possible ovarian primary site. *'They said 'We are going to treat you for ovarian cancer as that is the direction tests are pointing' so as far as I was concerned that was it. A plan was in place. Because I've got a plan I'm concentrating on that, not on the negative'*.

- The fifth theme was Healthcare professionals, not knowing the answers.

All patients referred to the healthcare professionals involved in their care as 'not knowing'. The majority of patients accepted this, whilst acknowledging that they would like more information.

'I do understand they're in the dark as much as me. They don't know enough about this unknown primary situation. Perhaps that is why they don't tell you much, because they're not sure of what they are telling you.'

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Some patients found it very difficult that the so called experts did not have any answers, one was worried that all the consultants were baffled and another said: *'You've got to let the doctors do their bit. I know it is difficult for them as well'*.

Most patients felt well supported by the healthcare professionals that they had encountered. A few reported feeling abandoned by their oncology teams. *'He said 'Well we don't particularly want you and ???????. Don't worry I will deal with you, even though it is not strictly my province''*.

- The sixth theme is the difficulty explaining to others.

Several patients felt that CUP was not like other cancers. Two found it difficult being told they were very young and very unusual to have CUP. *'It was quite upsetting that mine is a rare case'*.

Some patients found it hard explain CUP to their family and friends, whose own cancer experience seemed quite unlike their own. *'I keep getting the normal question 'Can they tell you where it is' and I try to explain but people still can't understand it.'*

One patient had not found that a problem at all. *'We've just told them that I have cancer, probably on the bone and in my lungs. I don't have any trouble explaining to people.'*

A few other findings from the study:

- Looking at people's coping strategies: Seven different coping strategies were identified and many, but not all of them, related mainly to coping with any diagnosis of cancer we thought. A recurring theme about trying to remain positive, about taking one day at a time, about how invaluable the support of family and friends is and the support of healthcare professionals, particularly when at home, so GP's and district nurses, who I don't think we have mentioned today, and palliative care services.

Some found talking about their illness helpful, others didn't. That is no surprise – dealing with any cancer is a very individual thing.

Many talked about the need to maintain a sense of control, and we got the feeling that these people had a greater quest to achieve a sense of control than, perhaps, some other patients with cancer that we see. They seemed to be particularly keen to get on and organise their affairs and make their own decisions.

- Other concerns were related to presenting with metastatic disease, which again makes enormous sense. The disbelief and shock lasting long after the initial diagnosis.
- Anger and existential concerns, particularly about the 'Why me', 'Why am I the one?' that people cannot find where the cancer's come from. The point was made earlier, by one of this morning's speakers, that actually it is not that rare. I think the patients found knowing that information helpful. Clearly fear of the future and the unknown.
- There were concerns about becoming more dependent, about role changes, impact on holidays, troubles about insurance for going abroad, and there were descriptions of patients healthcare experiences which, again, to us seemed to be not that different from other patients that we talked to day-to-day, but several did talk about being on a conveyor belt and that very much related to the diagnostic series of investigation after investigation, particularly when under the general medics or the general surgeons.
- All the patients had a desire for a diagnostic label, perhaps most quintessentially shown by the lady with possible ovarian cancer, who really jumped onto that and that was her coping

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strategy. *'It must be from my ovaries. That is what we are going to treat'*. Patients varied in their ability to cope with uncertainty and we found no relationship between the time from diagnosis, the extent of disease, the physical symptoms or performance status on ability to cope. Very importantly we found no relationship between the global quality of life scores and how well people perceived themselves as coping or not. So a word of warning for any studies with best supportive care in to first think about what best supportive care is, but also to think about how you measure quality of life.

- We did not assess personality styles. We have gone on to write a funding bid, which has been successful, for a much bigger study, which will assess a variety of things, including personality styles and will follow patients longitudinally and will have a more robust purposive sampling. Interestingly we were successful in our funding but the local research ethics committee have turned it down saying that they remembered approving this study by Lucy Boyland and me and they did not think that in this vulnerable group of patients there was a need to do any more such research. So I could give you their address and perhaps you could all write to them!
- All the patients described undergoing multiple investigations with little benefit.
- They all wanted more information but perhaps some did not realise that the information that they sought just wasn't there. The answers to their questions just weren't there.
- For some they said that this research had been their only opportunity to discuss how they really felt about having this diagnosis and they really valued that.
- Going on to some other things that specifically relate to having CUP, most wanted to know how CUP arises, how common it is, why the primary can't be found. Some of the things we have heard today can help. Those of us, who are not as skilled as others may do it better from now on.
- Most wanted as much detail as possible. They had a real desire to see their X-rays, see their scans, see where the tumour was hiding in their body and they wanted more information about other people's experiences of having CUP.

The paper is written up in the journal, Palliative Medicine. We did send it to some of the oncology journals, but I think it is understandable that a small pilot study of ten patients was not big enough but it was a shame, because we would far rather have put this into the oncology domain than the palliative care one.

Here are two mice. I think the mouse leaning on the bandage tin is Mr Mouse and the other one is Mrs Mouse. Mr Mouse has got tummy ache, maybe he has even got swine flu, and Mrs Mouse is making it better. She is sticking a great big sticking plaster on the bit that hurts and giving it a rub. I expect Mr Mouse will feel better. I use this point in my talk just to talk about this business about the uncertainty and about this need for visualisation. Because I think that what the patients were describing to us was that, unless they knew which bit was the bad bit, the treatment, and the clever experts, couldn't target at that and they couldn't target their coping strategies against it.

I looked up the word 'uncertainty' online - confusing, unsure, speculative, puzzling, inconclusive, equivocal and ambiguous. On the whole human beings don't cope with uncertainty very well. All patients with cancer have to cope with uncertainty but perhaps some have to cope with it more than others.

If you Google 'cancer of unknown primary' there are more than 1.5m references. Which rather surprised me, but the ones that I looked at were the Cancer Help, Macmillan and Cancer Help UK. They all acknowledged the uncertainty and how that can cause challenges for peoples coping strategies.

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I would like to move on, in the last few minutes of my talk, to talk about the role of specialist palliative care services. Clearly specialist palliative care services don't have a monopoly on caring, they don't have a monopoly on symptom control, they don't have a monopoly on commonsense, they don't have a monopoly on providing emotional support. They can do all those things alongside others, who also have those attributes, other health and social care professionals. So here is my list of some of the things that I think are the role of specialist palliative care services, particularly in people with cancer of unknown primary and their families:

- Emotional support for patient and family, not once the diagnosis is established but alongside the investigations and whilst they are going through the rollercoaster.
- Encouraging the development of coping strategies.
- Symptom management.
- Being alongside the patient, perhaps particularly in the acute hospital setting, but not being one of the oncology team, not being one of the day-to-day nurses or doctors. I learnt this the hard way back at Barts. I trained in medical oncology at Barts to do palliative medicine and they tried to turn me into a test tube shaker but did not quite succeed. I remember at Barts the hospital palliative care team going to see patients that I thought I knew really well and coming up with things that I thought they should have told me, or could have told me, but didn't. That is the real world. People choose who to say things to, for instance: a patient post bone marrow transplant, who's been in isolation for two months and is really beginning to wonder what the hell happens if this does not work and when my blood count recovers I've relapsed, sometimes feels so much part of the team of people looking after them that they don't go and say that to the haematology doctor, or even the haematology nurse specialist. They sometimes say it to someone different, who is in a different team.
- An advanced care planning, something around hoping for the best, but being prepared for the worst.
- Influencing clinical decision making.
- In the UK there is enormous focus at the moment on developing acute oncology teams to get the oncologists out to those patients admitted to acute hospitals throughout the land, who have been investigated for possibly having cancer, to put the expertise, quite rightly, into that, so that the right tests are done in the right order, at the right speed. That is about diagnosing people who need active anti-cancer treatment and it is about diagnosing the people and whom that would be inappropriate for. I feel very strongly, as do some others who I have talked to during the morning, that acute oncology teams need to be acute oncology and palliative care teams together.
- Other roles for specialist palliative care service are about supporting primary care services, through avoiding inappropriate acute hospital admissions, but also facilitating appropriate ones.
- There are very few palliative care people in the room. Every clinical person in the room will do palliative care as a large part of their job, the only difference between us, that specialise in it, is that it is our sole focus and our expertise. I can remember advising GP's on the telephone how to do a neurological examination to decide whether somebody might have cord compression or not. Quite a number of GP's ring up specialist palliative care services, even when we do not know the patient, to talk us through someone and say '*I don't really want to send them into hospital, but what do you think?*' and I think that in this subpopulation of people with CUP we have a particularly important role but the importance of communication has been flagged up really well by the pathologists through the morning, and this too will only work if there is really good communication between everyone involved.
- Hospital palliative care teams are very good at reducing the length of hospital admission. I feel that there is less of a need for that role on the oncology wards than there is on the care of the elderly, the general medical and general surgical roles. We were very proud in Southampton recently to win one of our strategic Health Authority annual awards. We won the Transforming Services Award for a project called 'There's no place like home' and that was about recognising upfront and checking that other people recognised and agreed too, that there were patients in the hospital for whom active treatment had become futile, who had

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between hours and days to live but who might prefer to die at home. Clearly we have a role in terminal care and bereavement support.

I would like to finish with a quote from the Jo's Friends website: *'People sometimes associate palliative, or hospice care, with end of life and it can seem scary but is actually very supportive. CUP patients should seek the support of a palliative team or nurse whether they are still receiving treatment or not. Currently I make very little use of the palliative care services but initially I was more reliant on the palliative care team than oncology'*.