

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

**Expert Panel:
What does Molecular Profiling add to the conventional
management of the CUP patient?**

Harpreet Wasan (Moderator)

Gauri Varadhachary (Case study presentation)

Tony Greco, John Bridgewater, Daphne de Jong, Christophe Massard, Richard Osborne, Karen Oien, James Mackay and Eugene Halligan.

Harpreet Wasan - Thank you all for coming. I would ask Gauri Varadhachary to present a case study, after which I will ask the panellists (who have not seen the case), to make specific comments on how the case was managed and any issues raised in relation to what we have been discussing.

Gauri Varadhachary presentation:

The initial question was: 'Which case to choose?', because it is such a heterogeneous presentation and there is so much going on. The case chosen is not to show that there is one right answer for the questions that we are asking, but hopefully to generate some discussion.

This patient is a 56 year old woman, otherwise in good health, who presented in 2004 with pelvic and back pain which became progressively worse over six weeks and was associated with urinary hesitancy. This troubled her and she saw her gynaecologist. On physical examination the gynaecologist could feel a pelvic mass. The Ca 125 was 72ng/ml. She underwent a CT scan and a transvaginal ultrasound which showed a large, 12cm, ovarian mass. There was no evidence of ascites, carcinomatosis or other metastatic disease.

The CT scan of her pelvis showed a heterogeneous mass abutting the uterus. Her past medical history was significant for a history of breast cancer in 1995, about 9 years ago, for which she underwent a modified radical mastectomy – two out of 10 lymph nodes were positive – she had adjuvant chemotherapy and radiation treatment. The tumour was ER/PR +ve and she was put on Tamoxifen for five years.

She saw a gynaecologic surgeon and underwent a total abdominal hysterectomy, bilateral salpingo-oophorectomy (TAHBSO), appendectomy and partial omentectomy at an outside institute. The pathology report showed:

- a metastatic adenocarcinoma consistent with a GI origin
- her lymph nodes were all negative
- the fallopian tube was negative for cancer
- the left ovary was negative for tumour
- there was no tumours present, except for the one in the right ovary
- the right gutter peritoneum had no tumour
- the right pelvic lymph nodes had no tumours
- the appendix was clean
- there was no tumour in the soft tissue and sigmoid colon removed during surgery

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The tissue got to MDA Anderson some time after the original surgery, as the 2004 surgery was not at MDA Anderson. The pathology was read at MDA Anderson, who made the following comments:

- The immunoperoxidase stains performed at the outset institution showed the tumour cells to be:
 - positive to cytokeratin 20, villin and CDX2
 - negative for cytokeratin 7, Wt-1, ER and PR
- suggesting metastasis to the ovary from the GI tract.

This patient underwent a colonoscopy a year before her surgery, which was negative at that time.

Such a patient presents at your clinic and she has had one ovary removed (in this case the right ovary with its tumour), she has a history of breast cancer nine years ago and the question is: 'What treatment is required now?' Do you:

1. Go in to do a better omentectomy and some intraperitoneal chemotherapy with a gynaecological, clinical trial. In other words basically treating this as ovarian cancer. One ovary was involved, she has a history of breast cancer and she also had a family history of breast cancer, so could this be a **brackup** patient?
2. Are you going to give the patient Paclitaxel and Carboplatin? Should you not get too worried about the immunohistochemistry ?
3. Should you tweak this with 5-FU and oxaliplatin in the stage 4 NED adjuvant therapy?
4. Should you just observe the patient since you really do not know if anything will help her at this time?

Harpreet Wasan: Thank you Gauri. Can we ask Karen what your views on the pathology of this case so far are?

Karen Oien: I think that the classification according to the **reneck** criteria would probably suggest that this was actually primarily ovarian in terms of the size, but in terms of the immunohistochemistry it is far more classical of the GI. Did you say whether it was mucinous? I assume that it was to have that histochemical profile. Was it mucinous rather than syrous?

Gauri: They did not comment on that.

Karen: Normally one would assume from that immunoprofile that it would be a mucinous and, therefore, regarded as potentially a met from a GI and/or that it should be treated as such. So there is a difference there already, between the different criteria. Personally I would go for GI.

Harpreet: Any comments on that from the panel?

Daphne de Jong: We would take a similar lead in the approach of this patient and probably come to the same conclusion from a pathologists point of view. This immunophenotype, which is very well evaluated indeed, points to a GI origin.

What I am stuck with, however, is that there is a discrepancy between the clinical presentation and what we, as pathologists, would suggest. When you look at it from the biological point of view actually the human cells are more plastic than this, very fixed approach, of all this set of proteins really represents. Indeed, tumour stem cells usually develop along their expected differentiation pathway but sometimes they take another route and, indeed, from the stem cell that might have been ovarian. From that start another differentiation direction can develop into, for instance, a GI differentiation and indeed there you see them, the GI proteins and looking at it from a gene expression point of view you would see a GI expression pattern. Logically those are the MRNA's or MIRNA's that eventually will lead to that protein set up. So yes, indeed, I fully agree that from a pathologists point of view you would come to the conclusion that it is GI origin. From a biological point of view it might be debatable.

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Harpreet: Sticking to the pathology I would like to challenge both of you and say : ‘If you say GI origin to an oncologist that means a lot, because there are different treatment options across the whole of the GI tract’. Would any pathologist like to comment on that specific aspect?

John Harvey, Lincoln County Hospital: Tumours break rules, if they all differentiated along the pathway that they were supposed to they would not be tumour cells. So plasticity is patently obvious. From a practical point of view if you see a mucinous carcinoma in the ovary it could be a primary or it could be a metastasis and it is a brave pathologist who will come down one way or the other and say, because of x it has to be this. It is a well known pitfall that you write down that ‘this is a primary mucinous adenocarcinoma’ and then at the MDT the surgeon tells you ‘I’m glad it has nothing to do with her colonic cancer’. Sadly it does! So from a practical point of view the trick with patients like these is to investigate them to make sure that they don’t have a gastro intestinal primary. There isn’t really much of a way around this in my opinion. I don’t think anyone else would argue. That is what happens at the coal face. These patients end up having top and tail tubes and a finger in their bottom and that’s really where you go.

Harpreet: There are two problems now that we have generated:

1. Who dares to call this a mucinous adenocarcinoma of the ovary?
2. Where in the GI origin is this come?

The pathologist might be happy if all the GI tract investigations, including small bowel and capsular endoscopy, are completely normal for us to call it GI. So that creates a bit of a challenge.

Any other views from any other pathologists as to whether this is an upper GI, lower GI or a mucinous adenocarcinoma of the ovary? In our MDT’s at the Hammersmith all the mucinous carcinomas end up coming to the GI team and I am always struggling with this.

Gordon surname not given: could not hear his comments at beginning

The best criteria, never mind the immunohistochemistry, in a metastatic GI colorectal to the ovary is actually necrosis and I know it is crude, but often if that is very extensive it usually points to colorectal origin. From a practical point of view you would almost certainly do a colonoscopy in this case.

Harpreet: This highlights a third point: we have already had two comments that the pathology report is inadequate.

Gordon: We have not seen the H&E or anything yet. Karen asked about that and that is a starting point.

Harpreet: In the short time we have it highlights the problem that when you get referrals and you cannot see the pathology and you get comments, there is no quality assured data set that everyone would agree they need for their assessment.

I would like to come back to Daphne for a moment for her comments.

Daphne: That fits to what you said. Obviously for a pathologist the whole thing starts with an H&E section. In general, of course, there are some exceptions. Metastatic colon cancer looks different from primary mucinous adenocarcinoma of the ovary. There it starts. Your level of suspicion of either a metastasis or a primary mucinous carcinoma is already different, based on the H&E section. We have only been shown the immunohistochemical results but we have not a single description of what it looked like, which to pathologists would have been very important. I think that Karen agrees there, as do all the pathologists in the audience.

Harpreet: The question I would ask Karen is: ‘If you sent this sample on morphology to ten pathologists would they all agree?’

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Karen Oien: I have not seen it, so I would have no idea.

Harpreet: In the generality of this sort of specialist opinion that we have to generate, we have a comment that the morphology and the experience of the pathologist is extremely important and I want to know how you standardise and quality assure that.

Karen: You heard me mention the ovarian mucinous tumours in my talk twice, as being a conundrum and difficult, so I suspect that answer would be 'no'. You would not necessarily get agreement. You would probably, hopefully, get agreement on the fact that it is an ovarian mucinous tumour. What you might not get agreement on is basically what it is doing there. Is it likely to be primary or secondary? Really there are a lot of criteria that have been alluded to, both by **Renette** and colleagues in terms of gross description and also the immunohistochemistry. I think, for the purposes of discussion, you are trying to get us to go down one side or the other!

Harpreet: What we are highlighting is what we struggle with every week actually. This is the problem.

I would like to extend the discussion to some other aspects. Move away from the pathology for the moment and move to treatment aspects and maybe integrating what you hear with the treatment choices that you have.

Tony Greco: I think that if this patient had an obvious gastric mass adenocarcinoma or colorectal lesion you could demonstrate there wouldn't be any doubt. It could be a so called krukentberg type tumour with metastatic disease to the ovary. The fact that the patient doesn't have that obvious primary site is what we are talking about today and the issue of whether this is a mucinous tumour of the ovary as a primary, or a metastatic from an **occult** site is really the issue we are talking about. This is precisely where I think that molecular diagnosis can help us. But getting to the points already made, the molecular diagnosis may tell us that this is bowel cancer when in fact it is mucinous cancer because cells don't necessarily act differently and there are only so many markers in these cells when these lineages divide and decide what they are going to be. You open a major Pandora's Box about unknown primary when you talk about cancer stem cells. Maybe Gauri is going to tell us what happened to this patient later, but in reality I would go along the lines of treating such a patient with a GI origin in mind because I think, in most cases like this, you are going to be right. Could this be a mucinous tumour and should the patient receive number two? I can't be sure. I would definitely get a molecular essay on this patient, which may help.

Harpreet: Thank you. Would you like to comment?

Eugene Halligan? As a molecular pathologist I am a passenger on this committee in terms of diagnosis but we could offer a quicker diagnosis perhaps if it is a CUP pathway. We are doing tissue of origin assay and their feedback is not so much on the prognostics and the outcome for the patient but the speed with which the diagnosis is made. The next action to take afterwards, if it is colon, then we can offer another molecular pathology profile perhaps on drug resistance or treatment regimes.

Harpreet: What I would like to say to you is that obviously there is an incredible opportunity here to incorporate this now in routine assessments of patients but the tests that you offer and the way that you give results back has a major impact on how we actually respond to that. So the first thing is that if you gave a list of five probabilities of what this tumour is I would say that, to me, that choice is clinically non valid because it does not help me at all. In your reporting of that molecular pathology, or the molecular assay, do you say that we are certain that it is, with a certain probability, this tumour?

Eugene Halligan? We are about half way through a trial at the moment and what we have chosen to do – our Ethics Committee has driven us down this line – is to look at non primaries but we are

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blinded and given the secondaries. So far the diagnosis has been a hundred percent. I take the challenge that I think the other chairman issued, that wanted a head to head comparison and see which is the most clinically useful and which is clinically irrelevant. So far, and we are not using these **to ..that's** how we got the ethical permission to manage patients, but the diagnostic profile has been very clear cut so far – there is no three way split in terms of probabilities. They have been in the high 90's in terms of the probability of what we would have, in all but a couple of cases.

Harpreet: Thank you that has been very useful.

Dorik Aubi, Mastergenics: We also developed such a classifier and I have to say that our approach is to use a chip that measures everything. So it is an **ephedra** metrics chip measuring 54,000 transcripts. The nice thing of that type of way of looking at things is that when you realise that you looked at too few pieces of information you can just add on. In this case when the question would be 'would there be a mucinous aspect in there?' you have every single mucinous gene already measured. Not only that but you have every single gene normally expressed in colon and gastric and gall bladder and pancreas, so from the picture of everything it becomes sometimes clear, even if it is a mixture, even what Daphne said about stem cells differentiating, even the level of stem cell mass in the tumour is there because most stem cell markers are known. So our classifier at the moment is using 6,000 genes, with a possibility of looking at any other, because you measure everything. From all genes it is very often, but still not always, possible to get all the information you would require too, and we call this to molecular **enceli** code dissect the tumour because everything you ask has been measured.

Harpreet: The question I am really asking, as a clinician, is 'Do you report one favoured diagnosis?'

Dorik: We report, depending on what you require, a whole score of categories. For example, in this case, most likely the digestive system would have had the highest score, but digestive in this case might also mean stomach or gall bladder and you would like to see the highest of all those. Our classifier reports what the clinician wants to know, so if you want to know all categories in there you will have many hundreds, even the proliferation state of the cell, or whatever.

Harpreet: I would like to stick to diagnosis. I need to focus on the point I am raising, which is not quite being answered. The question to all the companies and all the people involved in this: 'You have heard here that we can make a clinical judgement straightaway and that we have got three categories. So if you come back and confirm those categories you might find that your test actually has no utility in the future. What we want is, when we are really unsure, that we get a challenge that it is actually different to what we are saying. We want clarity on that. We do not want 40% chance of x, 35% chance of y, 48% chance of z. What I am trying to say to you is: 'How do you actually report it? Do you report one diagnosis, or do you report multiple diagnosis?'

Dorik: In our case you get a couple of hundred of scores of categories. So you will see the epithelial nature of the tissue, you will see each of the several cell types, so it is just like the pathologist looking at the molecular information and looking at the tissue.

Harpreet: I am going to get some clinical views on this because this is really the crux of the utility and I do not think we are necessarily getting straight answers on this.

Arwardi, Shrewsbury: Did you have any results from the CEA?

Gauri: It was normal.

Arwardi: Did you do any immune standing on CEA and CEA 125 in this specimen?

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Guari: This was not done.

Arwandi: As a clinician with this patient where you have got CK20 positive, CK7 negative, a mass and a pathologist review that this is a GI origin, this is a straightforward metastatic colon cancer, based on the CK result. I would treat on this, unless someone can prove something different. But based on the information in front of me there is CK positive, CK negative and a pathologist tells me that this is metastases. There was no ascites with this large mass in the pelvis. Even if she was a man I would have expected this CEA 125 to go up to 72 with this large mass in the pelvis. So there is no need to think about ovarian cancer in this case.

Harpreet: I would like a couple of comments from clinicians on the aspect that we raised about the uncertainty. If you have got uncertainty with pathology and clinics and the molecular analysis creates a little bit more uncertainty I am not sure that it helps.

Unknown-panellist?: I think that what we have to do is to consider the patient. Harpreet has just mentioned uncertainty and that has got to be discussed with the patient. There is a range of things one could do in this situation from a panel of molecular investigations to the test that I would favour, which is the test of time. If this patient has got metastatic GI cancer, then that is going to manifest itself at some future point. If this patient solely has stage 1 mucinous ovarian cancer, for which the benefits of adjuvant therapy are modest at best, there is an argument for doing nothing which does not appear on here. (Note: described as 'observation' on Guari's presentation). I think that before getting ahead of ourselves and deciding what myriad of highly sophisticated tests need to be done one would adopt a different approach in one patient, who was absolutely certain she wanted the best answer tomorrow, and another patient who, when presented with the limitations of what is achievable for both of these range of diagnoses, might elect to have a more hands off approach. So clearly there is no right answer but I think that one should think very strongly about the more relaxed approach to dealing with these patients.

Harpreet: We have some consensus here that everyone is going for a lower GI origin of tumour. No one seems to have objected to that?

David F??, Cheltenham: Could I ask the clinicians amongst the panel to commit themselves at this point to what treatment they would offer this patient. Dr. Greco has said that he would probably treat it as GI, but does he mean that he would use option 3 (5-FU and Oxaliplatin) or would he use 5-FU, ???, **Tecan** and Avastin if he is really convinced that this is colorectal cancer? But I wonder if the clinicians would commit themselves as to what treatment they would use and tell us what drugs they would offer this patient at this stage, before we go any further?.

Tony Greco: I think the observation is reasonable. I wouldn't do that because this patient is not a classic adjuvant case, but there is no clinical disease. This patient could still be a curable patient with GI site specific treatment. I would not use a **vast**, and in this instant, you may not use that here anyway. We don't have data in the 'adjuvant' setting that is useful. I would use a FOLFOX type regime in this patient. Although observation is not wrong I think that there is a small chance that you could cure this patient. You are not going to do much good if this is a mucinous ovarian cancer, which I do not think it is, I agree that there is marginal benefit for adjuvant there. I think that the answer is number 3 (5-FU & oxaliplatin) with FOLFOX.

Richard Osborne: If the patient was keen for treatment, with all the caveats about the uncertainty, then I would plump for a GI type tumour and would, hence, treat them along the same lines as Tony.

Harpreet: I would agree. I think that the issue you have raised is very important, because this is technically not adjuvant. It is metastatic disease.

James, is there anything else we could do to try and elucidate what is going on outside the dimensions we have just spoken about?

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James Mackay: I think that there was a very quick mention in the presentation about this ladies family history – she had a strong family history of breast cancer. That would be the first thing that I would be interested in hearing about. I think that we have a patient who presented with breast cancer at age 43, so I would be interested to hear about the family history. If there is a history of breast cancer and we have a 43 year old, who had developed breast cancer, who has now got a mass sitting beside her ovary, I think I may be the only one on the panel not heading towards a GI direction.

Stephen Faulk, Bristol: I am an oncologist. I would worry hugely about labelling this as a GI metastases, despite the Immunohistochemistry, which is actually the only pointer that is saying it is a GI. We would think colorectal with it being CDX2, CK20 +ve, CK7-ve, that is how our MDT would interpret it, but then I would worry. Colorectal cancer, where you cannot find an occult primary with a colonoscopy and there is no other evidence of **translomic** spread on the pathology that we have seen, a large ovarian mass in a relatively young woman, it does not add up to me.

Harpreet: That is a very valid comment. I would also say that another way of approaching this might be to say ‘Where are the advances in patient benefit and the biggest differences in survival to the patient?’ So you take it from the patients aspect and say ‘Why wouldn’t you do a herceptin test on this patient?’ We have now got data from gastric cancer, we have got a huge improvement in survival in gastric cancer, with a subset that are HER2 positive, we have a patient with a history of breast cancer. Why wouldn’t you just do that – that might make the biggest difference to this patient? You take the latest advance and you apply it to the current patient.

Tony Greco: I did not hear everything you said.

Harpreet: Let us say that there has been a breakthrough this year, which is on herceptin in gastric cancer and you don’t know where the origin of this is, but it might be a hugely, highly expressing HER2 +ve tumour. Would you now want to tailor that patient’s treatment? Which is the future of where we are going?

Tony Greco: I think you are bringing up an important point. Not necessarily that specific, but the fact that targets that are valid, where we have survival data, are treatments we are going to use in the future that we can learn from.

I would like to know the molecular profile done on this patient. It is important. Does the molecular profile support GI or does the molecular profile support ovarian or something else.?

Harpreet: I am afraid that we are running short of time, so there is a question there that Gauri needs to address later. One more question from the floor first:

Anna Callaghan, medical oncologist: I hate to sound like the Health Authority, but let us have a whiff of evidence here. If we are calling this a single metastatic site from colorectal cancer, I am presuming that we will have done a PET when the colonoscopies are negative. Where is the evidence of benefit for adjuvant therapy in a single metastatic site in the context of colorectal cancer, outside some extrapolated benefit where colorectal metastases have been excised with curative intent? We are hearing off down the line of what toxochemotherapy are we giving the patient when I think that what we have to sit down and say to such a patient is that we do not have a wit of evidence that giving you chemotherapy will benefit. Maybe we should be rolling ourselves back and saying ‘OK, we throw these patients from one **gynaey** MDT to the GI MDT. Is the time to pull out the trial, look at appropriate chemo regimes in an adjuvant setting here? I think we are far too far down the road of ‘Lets do something’ when there is no evidence at all. I think that that has to worry us.

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Harpreet: Thank you for a very valid point.

I am sorry that we are going to have to move on, but I have to say that if I was a patient seeking nine opinions I would be confused more and more with each opinion! Let us know return to Gauri to finish off the story.

Gauri: Continuation of presentation.

The patient was treated at an outside hospital with Paclitaxel and Carboplatin for six cycles. This was given to her by her gynaecological oncologist, who believed that this was likely an ovarian cancer. A single mass colonoscopy was negative and he really did not want to pay too much attention to the Immunohistochemical markers. This was all in 2004.

Scans after six months of therapy showed liver metastases and a biopsy result was similar to results in her ovarian resection. It was a CK20 +ve, CDX2 +ve biopsy from her liver.

The patient then came to MD Anderson for a second opinion and she underwent a repeat colonoscopy. We do tell our endoscopists to look for flat adenomas and to be very careful while doing the colonoscopy to look for a small primary. The upper endoscopy was negative and she did not get a capsular endoscopy.

The question now is: 'What would be her treatment option? She has taken Taxol Carboplatin for six months.

Harpreet: Any comments from the panel?

Tony Greco: Now she has metastatic disease and I again, think number three is the treatment. We could be fooled by any one case, but if you see a hundred like this, this is metastatic colorectal cancer.

Gauri: Let me intercept for a second. We requested, for insurance coverage, for any of these drugs and it was denied because it is an unknown primary.

Harpreet: So there is another dimension to the difficulty of health economics and how we want to move forward, which is going to get harder with these smaller subsets.

Any comments from the audience relating to the treatment?

David ???: I think this illustrates an important point. We had the result of a test, which has been validated through decades, which is the HER pathology report and interestingly her treating oncologist ignored it completely and decided to treat it as ovarian cancer. When actually the pathology was saying that it was completely different. I think there is a valuable lesson here because we are all saying 'do a gene expression' but, if it is not going to influence the ultimate decision, I am not convinced of the benefit of all these wonderful techniques that we are hearing about.

Tony Greco: This is just one patient. You may be right about this patient, but when you take all the patients I am not sure we can make that statement yet.

Harpreet: That is an interesting point for discussion.

Patient with CUP: Listening to you all, the bit that scares me is that the medicine you want to give me stinks. It hurts like mud. Whilst you are faffing about there is something that needs to be said about the quality of life that I am going to have and that is really important. I guess some of the things I want a clinician to be saying to me are accurately what the side effects are going to

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like and whether doing nowt allows me some quality of time rather than chasing round here to actually fall off the mortal coil but having had a lot of toxic medication.

Harpreet: Thank you for that reality check and making the point that you have to give all the options to the patient.

Because of time we will just ask Gauri to complete her case presentation.

Gauri: The patient was treated with the FOLFOX and bevacizumab at our institution. We think the immunochemistry with this profile is sufficient with this programme. It required a peer to peer review to give the patient oxaliplatin and bevacizumab in a metastatic setting without a colon cancer.

A slide of pre and post chemotherapy scans shows a good response to chemo. Over time she probably had some base line liver disease. So over time with oxaliplatin there was some liver damage. At some point there was a consideration of an extended right hepatectomy.

Following the colon programme, after eight cycles of therapy she was put on maintenance 5-FU and bevacizumab and over the course of the next two and a half years was treated with the colon cancer irinoterium . She did get the cetuximab. The Kras data was not available at that point. Oxaliplatin was reintroduced at this point. The patient succumbed to this cancer eventually, after forty months, with carcinomatosis. Her molecular profile, as part of a clinical trial, showed 99.2% probability of colon cancer and a repeat colonoscopy, three years into her treatment, remained negative.

The questions raised are:

- Should colon cancer profile CUP be characterised as a new ‘favourable’ subset?
- Is there enough data, as we stand today, with immunohistochemistry and **ore** profiling, to allow these patients to get the benefit of colon cancer therapies including biologics?

Harpreet: Thank you very much Gauri. I think that you have brought up at least twenty conflicting issues, which is absolutely the right way we have to think about all the problems that face us week in and week out with patients like this.

I would have to say, at least at this particular case, despite the confusion that was generated, the majority of the consensus was to treat it as a colon cancer and so, through the moral maze of the difficulty we had getting there, it was at least from the treatment point of view, the right decision for this patient.

Any additional comments from the panel?

Tony Greco: Can I just say one thing. This case was unusual in that there was an ovarian lesion but metastatic disease deliver without a primary site is not unusual, in fact it is common. If the patient has this type of profile is one going to ignore this and not treat with site specific treatment? I think not. With all due respect to quality of life the median survival for metastatic colorectal with no treatment is four to six months. With treatment the median survival is now approaching two years. Some patients do well for years without treatment but just follow ups after the initial treatment. This treatment for metastatic colon cancer, even though it is difficult, for many patients is very useful and so we do not want to just not allow them the opportunity to understand that. If they choose not to take treatment, of course we respect that.

Harpreet: That is a very valid point. If we can do that in the structure of what was presented within the clinical trial we will actually inform our choices better as time goes on.

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?????????????: This is a question to the panel: ‘Who would routinely do a PET after the surgery in this sort of case?’

Gauri: There are two issues here:

- The role of PET in CUP in general
This was discussed earlier this morning.
- The role of PET in a patient like this.
The role is for patients who have high cervical lymph nodes presentations, squamous cancer, where you can help direct the radiation treatment and the PET results are positive in about 30% of patients, perhaps patients with solitary disease. Patients with a colon profile: we get PET scans on them if it changes treatment eg. If they are rendered disease free, either surgically or with treatment, then we may alternate a PET scan with a CT scan if the PET scan identifies early that may be helpful for surgical consolidation, otherwise I do not think it helps us that much, it is just lead time bias.

?????: Once again I come back to the point of patient individualised approaches and a patient like this may be content with observation but they may, particularly a young person with prior experience of cancer, be very keen to know every last thing about their disease and I think that that has to be factored in. A patient like this, who could be harbouring other small amounts of disease at the time of her ova-rational presentation, which would change her entire thought processes, learning that from a PET scan would be helpful as well. If little liver metastases had been evident on the PET scan at diagnosis, that would have changed your whole decision making process. So somebody like this, if they were in the least inclined to Aud-active treatment, I would probably do a PET scan.

Member of audience: I would like to come back to remarks made by the panel, that actually it started out with pathologists saying that this is most probably GI, and that that information was completely ignored. That, again, underlines the importance of communication about these patients and that, indeed, all the information should be put together and should be integrated. It worries me that information by the pathologist was not considered at all. Would you then, indeed, order a gene expression, or molecular assay, giving you a one single answer and not ignore that? Or would you rather be inclined to integrate that in your decision making. That makes me worried. Are we going to bias the way we look at this patient and increasing the costs of the diagnostic work when it might not be necessary?

The second point that I would like to make is that actually now a modern pathologist is, rather than just being a person who delivers a single diagnosis, one who delivers much more information than that. Indeed we are asked to give prognostic information and predictive information and that is what we are trained for and that is what we do. That is what you can expect of a pathologist and so what you can expect on a biopsy like this is not only the information – yes indeed this is adenocarcinoma – you will also get the information – yes, we assume this is GI originated, because we can do the immunohistochemistry. This is what we are trained for. Additionally we are also trained for, and can do, molecular assays in the predictive field. So in these **Karasputations** are determined within the laboratories of pathology and so in communicating with us you can ask for those assays, and expect those answers. So make use of it.

Tony Greco: I think that the panel agrees with you. I do not think you need to defend pathology. Most of us, in the audience, thought that this was likely GI, so we did take your information very seriously. In 2004 the doctor taking care of the patient didn’t agree with that – that is OK as we didn’t know. That was five years ago. I think that pathologists are fully respected as part of the team and need no defence.

Member of audience: One of the important things that I would like to stress is that the current policy is to build large pathology labs outside hospitals, often also commercial labs. Those have

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little connections to the clinicians that they work for, so communication is going to be more difficult and yet, with all these types of complicated patients that we encounter now, and all the possibilities we now have for targeted treatment, it is far more important to have that good communication. So indeed, we should be very active in the discussion in what the position of the pathologist is in the clinical work. How favourable it is not to have the pathologist within your hospital but have it outside?

Harpreet: Another good point and more food for thought that we can discuss over lunch and during the afternoon.

Thank you Gauri for the extremely challenging and controversial case and the panel for making their comments and the audience.