

"Clinical Application of P.E.T. in Oncology"

Vancouver, B.C. June 11, 2001

Conclusions and Recommendations of the Conference

Conference Co-hosted by:



This document is a verbatim report of the conclusion/recommendation sessions of the Conference.

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Opening Remarks

Dr Simon Sutcliffe, CEO and President of BC Cancer Agency:

Good morning. On behalf of the BCCA, a co-sponsor of the meeting, I would like to offer my thanks to all of you as participants, to the local faculty, and to the invited faculty for joining us today for what will be a very important part of the step towards PET becoming an available modality in BC. I would like just to give you a few comments about PET, more specifically so for our BC audience, to tell you where we are and where we need to get to. You probably will understand that PET has become an established technology for the diagnosis, staging, and restaging of a number of different cancer sites in the US, Europe and in Asia. There are of course other indications than cancer, including neurological sciences and cardio vascular, but today we are focusing on clinical oncology.

In the US, there has recently been an expansion of coverage for funding for PET studies, such that there are now six cancer sites that have well-covered indications. Those include lung, oesophagus, colorectal, lymphoma, melanoma, and head and neck cancer excluding brain and thyroid. This expansion of funding recognises the acceptance by the funding bodies that PET is a unique modality of imaging, and acts in a manner that characterizes the biology of the disease, rather than purely the spatial aspects of the disease characterized by other types of imaging modalities. In Canada, health system funded PET is only available in Quebec, to a very limited extent in Ontario, and possibly very recently also in Alberta. Health system funded PET to date has not been available in the Province of BC.

Our attention here in BC on PET, was focused in the early part of 1998 with an educational symposium. We were very fortunate in early '99 to have the Institute of Clinical PET and the Society of Nuclear Medicine hold their annual meeting here in Vancouver, and offer us the opportunity to have an educational symposium. Later that year, we were given money through a philanthropic donation for the specific purpose of gaining some experience with PET. That initial experience was done through referral of patients to the University of Washington in Seattle. In February 2000, we submitted a business case statement to Government for the implementation of clinical PET capability in BC.

In October of 2000, the IPET Centre was opened, and we diverted our PET cases still using the philanthropic funding to the IPET Centre. We now have 8 months of experience, and at the rate of referral now, we would probably be annualizing at about 600 cases per year. Based upon our business case assessment of 17,000 new cases per year plus the prevalence factor that we would rise from that, we would estimate that we should be probably at least 10 times that figure - in a fully developed and mature and unrestrained system that could offer PET capability.

So our major task today is really two fold:

1. Number one is to raise awareness and become knowledgeable about the appropriate usage of PET in clinical oncology, and to do that using our own local in-house experience over the past 8 months, but placed into the context of international experience, as reflected by our invited international faculty.
2. Our second task, and we must all be held to this, is we need to derive those practice derived indications, with the evidence where possible, such that we can put a submission before government that identifies the indications with PET that we believe should be

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funded through the publicly funded health care system. To the degree possible, we will need to explore the evidence in this meeting for those indications. We need after this meeting, to prepare that submission and put it responsibly before government and give them a mechanism for an accountable introduction of PET, with funding, that is appropriate for the introduction of a new modality - relative to existing technologies.

Today, we have a very full agenda, as you will see. It is essential that we deliver on this goal of getting the evidence of the indications out by the end of today, and to that extent you will find me somewhat a rigorous adjudicator of the time, and I would ask all speakers to observe that because we have a lot of content and I don't want to keep you here any longer than the agenda has outlined. There are two minor additions to the schedule: Dr Nick Voss will be joining Joe Connors on the presentation with regard to lymphoma and PET, and secondly, Dr Dianne Miller will be presenting some experience on clinical PET in Gynaecological malignancies during the period of the session 11:25 to 12:00 noon.

So with those introductory comments, I'd now like to call upon Dr Edward Coleman. Dr Coleman is going to give a presentation entitled “Clinical PET - current practice, future potential.” Dr Coleman is Professor of Radiology and Clinical Pharmacy at Duke University Medical Centre in Durham, North Carolina.

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Breast Cancer

Speakers

- ❖ *Dr Vanessa Bernstein: Medical Oncology, Vancouver Island Cancer Centre*
 - ❖ *Dr Simon Sutcliffe: CEO, BC Cancer Agency*
 - ❖ *Dr Peter Conti, MD: Associate Professor of Radiology, Clinical Pharmacy and Biomedical Engineering USC*
 - ❖ *Dr Richard Wahl, MD: Director of Nuclear Medicine, John Hopkins University*
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Dr Bernstein: (Part of main presentation)

So what should our BCCA practice guidelines be for PET?

- Funding for PET should be available for evaluating breasts that are difficult to examine by mammography or ultra-sound where there is clinical suspicion of disease.
- Funding should be available to evaluate patients for distant metastases if current imaging fails to identify disease and there is clinical suspicion or perhaps biochemical suspicion such as a rising tumour marker or increase liver enzymes suggest it.
- There should be funding to evaluate patients for response of therapy if it cannot be determined by other means and such knowledge would change patient management either by stopping them from receiving further toxic therapy, allowing more effective therapy to be started earlier or perhaps when patients have failed several therapies and are on to very expensive therapies, the PET scan might even be cheaper than giving them 3 of 4 courses of treatment to see if it is working.
- Finally the evaluation of internal mammary node and axillary nodes should only be done in the context of clinical trials. Thank you very much

Dr Sutcliffe:

OK. Lets take breast cancer now, obviously more controversial. I think we clearly heard: directive problem solving, which obviously is by individual indications. We heard evaluate breasts that are difficult to examine by mammography and ultra-sound, presumably where there is believed to be a serious risk of breast cancer, we heard the evaluation of distant metastasis where there is equivocation on other modalities. We heard evaluation of the response to therapy if it can't be determined by other investigative means and we heard evaluation of IMC and axillary nodes, only in the context of further clinical research studies; I believe that is the correct interpretation. I think with the directed problem solving everyone could be quite comfortable with that as an indication, with respect to the others the dense breast difficult to determine but with a suspicion on breast cancer. Any comments with respect, from our expert faculty on that indication?

Dr Wahl:

Well I guess that could open up a lot of patients to the study and I guess it depends on how much money you want to spend. I mean the number of women with difficult to

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Dr. Wahl (cont.):

evaluate breasts with risk, I mean I would suppose that anybody between 25 to 50 with like a mother with breast cancer with somewhat increased risk so. I would say, at least my own experience in PET in breast cancer would be these women's breasts would be quite difficult to evaluate as they are younger, the background activity in normal breast is higher and if one looked at the evidence specifically for smaller lesion detection and try to segregate out women with radio dense breasts, I mean I think that you might start running out of evidence, in other words, I mean clearly smaller lesions you do have difficulty detecting, and I think smaller lesions with higher background activity are harder to detect so I personally think that you could open up a lot of issues. And then the other issue is if you did find something, there is the issue of how do you biopsy it, once you identify it, if it is not identified by other methods. Now this is an interesting challenge and I think a number of groups have spent time trying to develop methodologies for biopsying FDG or PET avid lesions. But exactly how to do it is still not routine. So you can say you can say that well you go and do an ultra sound or something else and then hope you would find it or an MR and try to figure out how to biopsy that. But I do think that this a little more aggressive than I would be in terms of the indication if costs are really limited because I think it might have to be refined further to define an extremely high risk group of women and even in that group I think it might be better to it as part of a study - that is just my opinion. I should add though that in some women, women with silicone implants, there aren't a lot of patients with specific problems but I think that in that setting PET is probably a little better and there are a few more specific studies done. We have a paper in press coming out looking at the intensity of normal FDG uptake by age and it clearly declines in an age related fashion. So certainly some young women have fairly high SUVs throughout their breasts as Dr Shreve pointed out and that is why I am a little bit reluctant on the very broad descriptive use in that group.

Floor:

Simon can I make a comment, I would absolutely agree with that point, particularly if the sensitivity at best from reading the literature is about 85% probably less for tumours that are T1 or so. You cannot avoid not doing a biopsy in these women with potentially curable disease should it be small enough. So I am not really sure enough how a PET scan if it is positive you are going to biopsy, if it is negative you are probably going to biopsy any ways, I am not really clear how PET scan in this specific scenario is going to help your clinical decision making, because the risks of not biopsying are too high in my own feeling.

Floor:

If I might add something to that as well, the PET scan sensitivity for axillary node and it seems the ability for breast cancer tissue is not very high. We have heard a lot of data presented today about FDG, has there been any work done at all with the other markers like the amino acids you know are there other PET tools that are more sensitive for picking up metastatic disease or identifying smaller T1 lesions in dense breasts for instance?

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Dr Wahl:

Well I think those are research questions and I think they are highly relevant questions but right now the small lesions are a problem even with dedicated Breast PET imagers which Paul talked about, phantom studies have shown that you still having difficulty in detecting lesions under one centimetre with the typical uptake levels seen with FDG. So I think that there is interest in looking at other agents which have a lower uptake in normal breast. The studies done with pyresene and methenamine and even thoresodial have been limited. They do show promise but they have been very small studies so I think they are too preliminary that you would want to try to adopt them routinely.

Floor:

Simon if I could say some thing, its Karen here, I think the whole breast issue is obviously very complex as shown by the fact that it hasn't been approved for funding south of the border in many ways and I think what we have come up with really is a bit of an individualized question. I think there is the question of we can't just abandon this tumour site obviously there are a number of situations where it is of relevance, but it is really an individualized situation of diagnosing otherwise difficult to diagnose areas. I think what Steven said is very important in terms of needing to biopsy anyways, I think what Vanessa summarised otherwise is very individualized cases of metastatic diseases not otherwise diagnosed and I think that at the end of the day we have to be very practical, that this is a place where we want to have some impact on our management, we want to use PET sensibly in those cases where it may impact on our management. This is a huge group of patients and therefore I think that we have to be quite responsible in doing it that way.

Dr Conti:

May I add also that next week we present our case to HCFA on Breast cancer the 19th June, and the, basically the discussions have been thus far to present two indications. One is in the dense breast surgically manipulated breast and the second one is in the issue of staging, excuse me in re-staging and detection of recurrent disease. Those are the two areas that we want to discuss with Medical Advisory Board to HCFA, next week. My own feeling on the dense breast issue is again an individualized approach, that in cases that are diagnostically difficult if you will, and some of those cases may or may not be amenable to biopsy, for example the presence of an implant, those types of cases; so you might want to consider – of course breast cancer is going to be one of the ones you are going to go after surgically and you are going to go after these cancers with biopsy and don't want to interfere with that standard of care to any great degree except where it is potentially well demonstrated that it can be avoided and not necessary.

Dr Sutcliffe:

Thank you Peter. It would seem that may be we have to take a fairly pragmatic approach to breast cancer in terms of indications and estimate a percentage complexity factor as being the determinant of utilization to answer to specifically directed questions.

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Central Nervous System (CNS) Tumour

Speakers

- ❖ *Dr Simon Sutcliffe: CEO, BC Cancer Agency*
 - ❖ *Dr Peter Conti, MD: Associate Professor of Radiology, Clinical Pharmacy and Biomedical Engineering USC*
 - ❖ *Dr Paul Shreve, MD: Assistant Professor, Internal Medicine, University of Michigan Medical Centre.*
 - ❖ *Dr, Dr Richard Baum PhD: Chairman PET Centre, Zentralklinik, Bad Berka, Germany*
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Dr Sutcliffe:

We are going to discuss the three sites that have been under discussion, that is CNS Tumours, Breast cancer and pediatric cancers. I think on the issue of CNS cancer there were clear there were two circumstances I believe that Paul recommended.

- ❖ The first being clearly recurrence versus necrosis as being a clear indication for the use of PET.
- ❖ Secondly: the use of PET to identify a site for biopsy, if it is not apparent on other imaging modalities. Those would appear to be the only two indications that were put forward at the present moment.

Dr Shreve:

Yes you might want to expand that it is not apparent on other modalities because those patients will have an abnormal CT or MRI, it is really a question of where you are most likely to get the highest grade of tissue. So it depends on the size of the mass and on the location I think.

Dr Sutcliffe:

Any further comment on that from other speakers or from the floor?

Dr Conti:

I thought may be you might want to rephrase that latter one because you might want to just consider in treatment planning or in biopsy guidance to make it more generic as opposed to presence or absence of modality findings.

Dr Baum:

I would add grading which is very difficult in some cases as shown and one should not only look at FDG one has to include the amino acids like C11-Methinene or we use F-18 Tyrosine. It is really very useful and very often requested to decide if to do aggressive therapy or just to wait and see so that is a very important clinical point.

Colorectal Cancer

Speakers:

- ❖ *Dr Helen Anderson: Medical Oncology, Vancouver Cancer Centre*
 - ❖ *Dr Simon Sutcliffe: CEO, BC Cancer Agency*
 - ❖ *Dr Peter Conti, MD: Associate Professor of Radiology, Clinical Pharmacy and Biomedical Engineering USC*
 - ❖ *Dr Paul Shreve, MD: Assistant Professor, Internal Medicine, University of Michigan Medical Centre.*
 - ❖ *Dr Richard Wahl, MD: Director of Nuclear Medicine, John Hopkins University*
 - ❖ *Dr, Dr Richard Baum PhD: Chairman PET Centre, Zentralklinik, Bad Berka, Germany*
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Dr Sutcliffe:

I am going to go back to colorectal cancer and I believe that we have two clear indications recommended: One in colorectal cancer is the detection of recurrence where conventional imaging methods are negative or equivocal and there is suspicion of recurrence either as elevated CEA or by virtue of patient symptoms.

Dr Conti:

Two points just to remember:

1. That the CEA is no longer a requirement by the HCFA at least in the United States as entry to being eligible for this procedure as of July 1, 2001. So as you all know many of these cases do not express CEA and therefore it is not a reliable measurable parameter for detecting either primary or metastatic disease.
2. The other thing that I wanted to mention is or pose almost as a question to the group is, if you are willing to use colorectal PET scanning for measurement of colorectal recurrence or assessment of patients with suspected colorectal recurrence why would you not be willing to use it to stage after primary diagnosis?

Dr Sutcliffe:

Helen, do you have any comment on that? Any comment from the floor on that particular question?

Dr Conti: I didn't think so.

Dr Sutcliffe: From the Panel?

Dr Shreve:

I guess one of the issues is, do you do any imaging staging for patients with primary colon cancer before the operation and in some cases the surgeons go ahead and operate and do operative staging before a CT scan is even done – I guess the question would be if you are going to do a CT scan for staging why not do a PET scan? That would probably be a better way to put it.

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Dr Conti:

I think if you are asking an anatomical question where in terms of surgical planning you need the anatomy then you do the CT scan irrespective of PET, but the issue really comes down to if you are willing to take the chance to rely on PET to detect recurrent disease – that might be surgically respectable. That is the same cancer in fact, that you started with - that you could have staged initially, that you could have made a difference in the initial management of the patient in terms of the original surgical approach perhaps? It may have had that liver metastasis in the first place, that could have been resected when it was only one instead of three say, at the time of recurrence. So, given the fact that it is the most sensitive test that we have, given the fact that is for colorectal cancer, given the fact that – it has shown efficacy in terms of its utility in deciding surgery or no surgery in the recurrent population. You should consider using it in terms of treatment planning up front after the initial diagnosis – not necessarily to make the diagnosis in colorectal cancer but to stage the patient.

Dr Sutcliffe:

So Peter you have agreed with the detection of recurrent indication but you are broadening that to say pre-operative staging prior to further management would also be the appropriate indication.

Dr Anderson:

That is very interesting suggestion that you have made. Is there any evidence that this has been done? Where do you draw the line in saying that the patient who has stage 1, early stage colorectal cancer their chance of recurrence is very low, what is the evidence? Which group of patients would you do these PET staging investigations for?

Dr Conti:

The answer is unknown – that is why I am asking you as a group. Are you willing to take the chance, based on the fact that the evidence is very strong in the other population? It is almost unequivocal that PET is useful in the issue of determining whether someone should be re-resected with recurrence, and given the fact that it is probably the same cancer, given the fact that there is avid FDG uptake in colorectal cancer, and given the fact that it is a surgically treatable disease, and if there was disease, that was resectable early on; it could have an impact on patient management and care and perhaps outcome. Why not do it that way, despite the absence of specific literature?

Dr Anderson:

Perhaps a better question would be: why does one not do a study looking at this particular question rather than just adopting it?

Dr Conti:

The answer to that is that we do it in clinical practice, many of us already and we are beyond worrying about this, we are into something else now that is what has happened. A lot of the PET literature is, it is not necessarily information that is published anymore. People have moved beyond doing some of these indications – they have adopted them as routine procedures, they are moving into other areas of investigation in the academic centres. There is no driving force to do something that you find already clinically efficacious to necessarily publish a prospective trial to prove it, the procedures have moved on.

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Dr Wahl:

Well I think that still it is probably publishable in primary colorectal cancer. Exactly what the role is I, there is not much literature there, much more literature in recurrent, and you know I think, certainly our colorectal surgeons are interested in this possibility particularly the higher the Dukes Stage -the more likely it is you have metastases to other tissues and potentially the liver, and clearly if you are going in to do supposedly curative surgery and lesions are in the liver and you don't know it, it is kind of not optimal. So there probably is a point where the lesion becomes high enough risk that it would have a high yield of being useful in this less invasive primary colorectal, it is probably not going to be a very high yield and certainly the issues of detecting small little metastasis are going to remain, I mean the physical limitations of detecting these lesions will remain with PET which will be better staged surgically. So I think Peter that you are right and a reasonable thing to do, but I also would agree that doing a few more studies on it would be probably pretty useful because most people are not using it primarily for staging.

Dr Sutcliffe:

I suspect Peter that no one has as philosophical or conceptional difference, we know that with a very conservative funding body which we will engage, the absence of evidence will be a detriment to getting that done. So we have discussed that indication. The other indication put forward was staging in patients who have potentially resectable recurrence is there any dispute on that or concerns with that indication?

Dr Baum:

I just would like to stress from our own data that in Frankfurt where we had several hundred of patients that were studied before liver resection of metastasis that it is a very good method of detecting extra hepatic disease especially if you plan for regional chemo therapy on lets say complicated regional resection of liver metastasis, central liver metastasis which are high risk and so on. It is a very good method to look at extra hepatic disease. In quite a number of patients you find extra hepatic involvement which was previously not known I still have a small criticism lets say, to the way you presented the role of PET in colorectal cancer, you said several times that there is not much data or very small data and so on, I would like, I don't know if you know this, this is the Supplement of the Journal of Nuclear Medicine, which just appeared in May. I would just like to make a citation of that: This is the summary of 1387 patients, 2444 lesions and sensitivity was 94% and 87%. I mean one might doubt if this is useful to make these summaries and meta-analysis but it is not a small number, several studies here include patient numbers of more than 100 and I think that it is a very good body of evidence in colorectal cancer and I was responsible in 1997 for the German Consensus Committee on colorectal cancer and at that time we already decided that there was enough data to justify that it is good for searching for recurrence and staging for patients who are planned for major surgeries so since then the data are much more robust.

Floor: *(original in Head and Neck Discussion)*

I just want to go back to colorectal, for a minute, the one recommendation that it be used in patients who are asymptomatic but have an elevation of their tumour marker there have been a number of studies published showing that there isn't any really definite benefit to following patients with tumour markers and it was my understanding that we are trying to educate the mostly community physicians to stop ordering CEAs, stop ordering CA15.3s, 19-9s in patients who have been treated for their disease. So I am just wondering how

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that recommendation ties in with that because I mean I certainly have been in that situation before where I have had consults coming in from family doctors that someone who had a breast cancer or colon cancer resected a few years ago and now their marker is going up and they end up with a million dollar work up and you don't find any thing.

Dr Baum:

I think that one of the main reasons to doubt about the usefulness of tumour markers was the lead-time of tumour markers because conventional imaging was not able to find and localize the tumour. Now I think this has exactly changed by application of FDG-PET at least in colorectal cancer, in our series and this involved several hundred patients there was if I remember only two patients with an elevated CEA where the PET scan was negative and this turned out to be brain metastasis of colorectal cancer which is quite rare, but where we missed it, but all the others had positive lesions so in my view it is very important to do tumour markers in the follow up of high risk patients especially Dukes C and so on, and to detect early disease especially single liver metastasis, which can be resected or single lung metastasis which can be seen and resected.

Esophageal Cancer

Speakers:

- ❖ *Dr Simon Sutcliffe: CEO, BC Cancer Agency*
- ❖ *Dr Edward Coleman, Professor of Radiology, Duke Medical Centre*
- ❖ *Dr Ken Evans, Thoracic Surgeon, Vancouver General Hospital*
- ❖ *Dr Ken Wilson, Medical Oncology, Victoria Island Cancer Centre*
- ❖ *Dr Paul Shreve, MD: Assistant Professor, Internal Medicine, University of Michigan Medical Centre.*
- ❖ *Dr Richard Wahl, MD: Director of Nuclear Medicine, John Hopkins University*
- ❖ *Dr, Dr Richard Baum PhD: Chairman PET Centre, Zentralklinik, Bad Berka, Germany*

Dr Evans:

So in summary Simon here are the indications I think we should be using PET scanning in thoracic malignancy:

- ❖ I think we should be using it routinely in the staging work up for carcinoma of the lung
- ❖ Getting back to the earlier presentation I think that we should be using it routinely in the staging work up for carcinoma of the esophagus in patients who are going to undergo surgery for radical treatment.
- ❖ I think it is important in evaluating indeterminate pulmonary nodules as Dr Baum mentioned.
- ❖ Finally, I think that it is indicated in patients with thoracic malignancy looking for recurrent disease.

Dr Sutcliffe:

We are going to enter a discussion session now on these two tumour site presentations lymphoma and esophageal cancer. Ken don't go away from the microphone or at least stay close to one. The panel session is an open session, an interaction with the audience our invited faculty and our local faculty and we want to get into a discussion on the indications that have been presented to us.

- Are they legitimate?
- Is there evidence associated with them what should we be recommending as current state of the art PET usage with appropriate evidence?

Maybe we will take esophageal cancer first, Ken you have put forward, you believe that PET should be used at the time of diagnosis of esophageal cancer for those patients who would be appropriate for radical surgery or for a chemotherapy/radiotherapy treatment plan; is that correct?

Dr Wilson:

Yes that is correct. The object obviously is to exclude patients who have distant metastasis from consideration of either treatment and to identify nodal sites perhaps which may be treated either by chemotherapy or by surgery.

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Dr Sutcliffe:

Perhaps I can pose that to our faculty, would you agree with that recommendation for indications?

Dr Coleman:

I certainly agree that that is one indication we have been doing more and more of those at our institution. Another one that I think should be considered is the evaluation of the patient after the completion of the chemotherapy/radiation therapy just to see what their status is at that point and I know at least in some, centres are considering these patients right now for surgery after the adjuvant chemo/radiation therapy. That is something that there is not a lot of data on but something that I know that we are starting to use PET scans for at our institution.

Dr Wilson:

As a matter of fact that has been our so called approved indications for doing PET scanning for esophageal cancer; there being a finite pool of money we were asked which categories of patients do you think we should focus our attentions on and having undertaken primary chemo or radio therapy on these patients – obviously there are two potential radical treatments; we have gone from the non surgical one first and then the scan is being undertaken to determine disease extent, disease activity and suitability for surgery; I agree entirely that that should be added to the list.

Dr Evans:

Esophageal cancer is such a bad disease and we are seeing more of it of course with the increased incidence of adeno-carcinoma, and I think that we are going to be seeing it in the younger age group to as related to reflux and what not and from the surgical perspective the surgery of course as major as Dr Wilson mentioned but the surgical results are improving and the mortality rates are getting lower and certainly we do not want to operate on anybody who is incompletely staged or who has metastatic disease and my feeling is that PET scanning should be part of the routine staging work up for esophageal cancer, as well as looking at recurrence after treatment.

Dr Wahl:

I would agree I think that data are incredibly strong that it is more accurate than your standard methods for determining whether the disease is localized or disseminated and I think in time we are going to be asking ourselves not the question of whether PET should be done in these patients where I think the answer is yes but the question of what additional information is provided by CT in these patients and I think that will be remain to be seen but certainly at Hopkins where there is a lot of esophageal cancer seen. We are basically doing PET on everybody prior to the initial decision on treatment to determine whether the disease is localized or disseminated so the data seem very strong – I would agree with you.

Dr Sutcliffe:

So you would be saying that at the time of initial assessment for a patient who is technically fit for surgery excluding other co-morbid conditions or general condition if they are eligible and fit for surgery you believe that PET is the standard evaluation?

Dr Evans: Yes I do.

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Dr Wahl: So do I

Dr Shreve:

I would have to concur at Michigan we see the same phenomena, where our surgeons are very interested in finding occult metastasis particularly the retro peritoneal and the super ventricular nodes that are not well detected particularly the super ventricular nodes on CT and it is becoming routine now to do the PET scan prior to surgery since obviously finding distant metastasis changes the management. Also again we found many times the abnormalities on the CT retrospectively particularly below the diaphragm just isn't called by our expert CT people.

Dr Baum:

I would like to stress a point that to use FDG-PET before radiation therapy, we have done a prospective study of about 60 patients together with our radiation oncologists and looked at the extension of the radiation field before and after PET and in a number of patients which is in the range of 20 to 25% there is much more extended field by the PET determined as compared to the CT alone. So it might be very useful before radiation therapy and also for looking at treatment response.

Dr Sutcliffe:

It sounds as if the general philosophy that is coming forward is again in the patient who is fit for operation with esophageal cancer PET would be the single most useful test in terms of evaluation of the disease and that one might argue, CT has relatively little role if you have access to PET in esophageal cancer. I am putting that forward for response or contradiction.

Dr Wilson:

I think old habits die hard it is difficult to believe that CT scanning for esophageal cancer would become extinct anytime soon. Perhaps the surgeons might address that? I am sure there is a comfort level with CT scanning.

Dr Sutcliffe:

Just before any colleagues answer, it seems as if we are saying we are looking for evidence-based use of practice. One would argue more strongly that there is less evidence for the use of CT than there is for the use of PET.

Dr Shreve:

Yes, I think that may be true but in the first place that anatomic framework of looking at the body will not disappear quickly and secondly this is something that we will be

Dr Shreve (cont.):

exploring more completely with the combined scanners the CT is often helpful in interpreting the PET scan and vice versa. So I'm not sure that we will be seeing the demise of CT for esophageal cancer more likely the technique we use to do CT in esophageal cancer will change somewhat and will be less aggressive in the use of contrast material with the advent of the combining the CT with PET.

Dr Sutcliffe: Are there any views from the floor? Tom.

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Floor:

I would just like to know why MRI is not figure in any of these comparisons as a diagnostic tool given its different characteristics – particularly MRI with cadmium and the manipulations that go with it?

Dr Wilson:

I don't know the answer to that question but in all the papers that I reviewed about PET scanning in esophageal cancer the standard the gold standard is surgery the other techniques are CT scan and esophageal ultra sound, MRI was not apparent in any of the studies. I think I listed about 20 of them of PET studies in esophageal cancer.

Dr Coleman:

In most of our abdominal imaging colleagues, most of our colleagues who are most familiar with the best way to image these anatomically feel that the new CT technique with enhancement is generally a better study than MRI. There are some circumstances where MRI may be a little better but the literature out there is mainly CT for evaluating most of these malignancies and that is the standard by which we are comparing. If MRI would have been performed in these patients the comparisons would have been between PET with MRI; but for most of these cancers CT contrast enhanced CT is the standard technique for evaluation.

Dr Shreve:

You know one of the problems with MRI is the motion in the mediastinum, with cardiac action and respiratory motion. Problems that have not been entirely solved and particularly with a multi detector CT those motion problems aren't an issue.

Dr Sutcliffe: Ok I think yes. Ivo?

Floor:

The fairly clear statement that if the MRI or the PET scan was positive and showed disease beyond surgical volume, that surgery would not be done but with these recommendations doing PET for all potentially operable patients if disease beyond the primary site was identified that being that radical chemo therapy radical approach would not be taken with respect to the chemo radio therapy? Would still be doing that might...

Dr Wilson:

The width of the radiotherapy field is in the hands of my colleague Dr Lim, Radiation Oncology and the feasibility of the safety, the feasibility of applying a wider field to cover patient, with a PET scan node positive obviously can only be done on an individual basis.

Dr Wahl:

I think it is worth clarifying that PET is remarkably accurate for staging esophageal cancer particularly for distant metastatic disease but it is not perfect and particularly in the study from the University of Pittsburgh there are some instances of false positives in particularly the mediastinum and faint uptake in mediastinum nodes may not represent metastatic esophageal cancer and I think that most reading scans are quite aware of that but if it is say small uptake in the mediastinum node it may well be, at least in my part of the country where I've lived in the US there can be patients that have had inflammatory disease that can cause faint uptake. Glucose is measuring glucose metabolism FDG is not

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necessarily always reflecting cancer so I think that still biopsy proof of metastatic disease if it is an equivocal PET finding not multiple foci for example may still be appropriate but certainly PET would detect and direct you to these areas in some instances it might still be necessary.

Dr Sutcliffe: Yes?

Floor:

I am just wondering if PET, I mean if radio therapy, alters the FDG uptake such that there should be an optimal time frame after radiotherapy to obtain a PET scan?

Dr Wilson:

I think that the jury is out on that question? There simply isn't enough information in the literature about the value of PET scanning post chemo/radiotherapy for example and the optimal time. Locally it has been done when the reaction has settled down usually after the patient has had a CT scan and follow up and an endoscopic examination follow up with a positive endoscopy obvious a surgical candidate.

Dr Baum:

After radiation therapy you have to wait at least four to eight weeks because you have a severe radiation induced mucocytis especially on the esophageal region which can also increase uptake in the upper lymph nodes so it is very useful to wait for a long period after radiation therapy this is not the case for chemo but for radiation.

Floor:

I get the sense that this is not be as accurate for assessing the presence of liver metastasis is that correct and if so what would be the preferred, should one be using it with CT or Ultrasound?

Dr Coleman:

Certainly PET is very accurate in detecting liver metastasis, I have not seen a direct comparison of FDG – PET to CT certainly in colorectal cancer you will hear later today, it is more sensitive and specific than CT and in detecting liver metastasis, from my experience I think the same is true for esophageal cancer but I have not seen it broken down but it is going to be very accurate for detecting liver metastasis so I would feel very comfortable with the PET scan.

Dr Sutcliffe:

So on esophageal cancer if I could summarize it would seem that we are saying; in the patient who is fit for surgery it would be recommended that PET be one of the, be part of the initial evaluation of the patient with esophageal cancer to exclude distant metastasis in a patient who is otherwise operable and for a patient who has undergone radical radiation therapy and chemo therapy and whom it is believed that further surgical salvage could be a potential option. Would those two recommendations be consistent with where the US is going?

Dr Coleman:

Certainly those are the primary reasons that we are doing PET scanning, both the Blue Cross/Blue Shield Technology Evaluation Centre, and the HCFA now will

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be paying for PET performed for diagnosis if needed, it generally is not used for the diagnosis but for initial staging and restaging which this would then fit into those categories. So yes.

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Gynaecological Malignancies

Speakers:

- ❖ *Dr Dianne Miller: Gynaecologic Oncology, Vancouver Cancer Centre*
- ❖ *Dr Simon Sutcliffe: CEO, BC Cancer Agency*
- ❖ *Dr Peter Conti, MD: Associate Professor of Radiology, Clinical Pharmacy and Biomedical Engineering USC*
- ❖ *Dr Paul Shreve, MD: Assistant Professor, Internal Medicine, University of Michigan Medical Centre.*
- ❖ *Dr Richard Wahl, MD: Director of Nuclear Medicine, John Hopkins University*
- ❖ *Dr, Dr Richard Baum PhD: Chairman PET Centre, Zentralklinik, Bad Berka, Germany*

Dr Miller:

So the questions we have from a gynaecological stand point regarding PET scanning are a little bit of uncertainty with regards to the sensitivity and I will say that almost all these questions haven't been addressed in the other tumour sites earlier this morning.

1. What volume of tumour is required for a positive PET scan? How does it differ in regard to tumour type?
2. Is there validity in the lower grade tumours?
3. Can it replace traditional imaging?
4. Is there a role in the follow up of patients particularly in those situations who have good second line treatment?

So we feel in our group that there is a huge potential in gynaecological oncology and that we do need to develop some protocols to validate the technique. Particularly as there is not as much in the literature regarding gynaecological tumours as there is in some of the other sites, And we believe that particularly in evaluating lesions in the pelvis that it may well replace some of the traditional imaging, and we also feel that BCCA would be a great place to test the validity of PET scanning in gynaecological cancer due to well established referral patterns and an excellent registry.

Dr Sutcliffe:

Thank you very much Dianne. Perhaps I could just go to our expert panel in two areas:

1. Why is the state of the art in gyny cancer not at the same place as in other solid tumour site, what is the reason for that?
2. Some comments perhaps on some of the discussion points that Dianne has raised.

Dr Coleman:

Yes, just to summarise some of the information that we have available. The data on cervical cancer and spread to pelvic lymph node and distal metastases actually is quite strong and may be stronger than some of the other indications that the HCFA will be evaluating in the near future. So I think its utilization in cervical cancer can be justified from the literature that is available to us at this point in time. The uses for the other indications are not as well supported, there is some data on ovarian cancer; there are one or two studies that I am familiar with, a hundred to two hundred patients at the University

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Dr Coleman (cont.):

of Tennessee, Knoxville. Dr Karl Hubner did a very nice study on ovarian cancer. The studies were suggestive that it may be helpful there both for the detection of spread at time of diagnosis but particularly for the detection of the recurrent ovarian cancer the timing of the second look surgery that you were talking about. The problem with ovarian cancer is that it is frequently very small sheets of cells, not in masses, so that makes it very difficult to detect that type of recurrence as compared to nodal recurrence where it is in a mass. You ask about the volume of disease necessary for detection, again it is like the lung cancer or the other malignancies that we talked about, it all depends on the uptake by the tumour and the surrounding tissue uptake to see if you can see it. Generally we are talking about lesions being somewhere between 5mm and 1cm for us to detect accurately but smaller lesions that have more uptake will be detected, larger lesions with less uptake will not be detected.

Dr Sutcliffe:

Thank you very much Dr Coleman. Any further comments from the panellists, or the floor, regarding gynaecological cancers?

Dr Wahl:

I think the data in ovarian for recurrence versus CT, although the numbers of studies are small, are fairly strong. I think, it is my opinion and there are statistical data in those papers show that for recurrent metastatic ovarian cancer PET is clearly better, I think than CT, even though those numbers are fairly small.

I was interested in imaging ovarian cancer quite a long time ago and at least part of the reason we moved onto lung and breast among other things was that the NIH decided to fund my proposal. I remember my proposal in lung cancer and one in breast and at the time did not agree to fund this ovarian work. It's sort of hard to know but I think some of the early studies weren't supported by our government, so you kind of have to do the work that you get supported to do - at least in the environment that I was in which I was located in but we saw promise to ovarian cancer early on in animal studies - it was one of the first diseases that we looked at in animals and in people and I think there is a lot of potential there.

Certainly 3 or 4 papers recently on cervical cancer; I personally think that it is the method of choice for staging local regional nodes for cervical cancer and I believe anecdotally that there will be a paper coming out shortly showing the prognostic value of PET in cervical cancer which I think is going to be quite useful as well, so I think that is one where it might well be said that these are infrequent less frequent diseases and it is hard to have the number of large studies done and if the data are compelling even in smaller studies I think, you are going to delay introduction of a useful technique while you are waiting for large studies in small numbers of patients, and I think that this is one of the concerns overall I have with the disease based approach to PET.

For patients who have rare tumours their diseases are just going to be infrequent enough that it is going to be hard for PET to get out and have large studies done; so at a point you have to, I think to make a decision for infrequent tumours that maybe if the early data are suggestive, that the criteria for making the technology available have to be more liberal

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Dr Wahl (cont.):

than in diseases like lung, where you can get you know, thousands of patients, where conditions like ovarian and some of the others are much less common - thyroid is just hard to get the numbers of patients done - just a comment.

Dr Sutcliffe: Argue strongly for this being a site in the provincial context.

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Head & Neck Tumours

Speakers:

- ❖ *Dr Helen Anderson: Medical Oncology, Vancouver Cancer Centre*
- ❖ *Dr Simon Sutcliffe: CEO, BC Cancer Agency*
- ❖ *Dr Peter Conti, MD: Associate Professor of Radiology, Clinical Pharmacy and Biomedical Engineering USC*
- ❖ *Dr Paul Shreve, MD: Assistant Professor, Internal Medicine, University of Michigan Medical Centre*
- ❖ *Dr Richard Wahl, MD: Director of Nuclear Medicine, John Hopkins University*
- ❖ *Dr, Dr Richard Baum PhD: Chairman PET Centre, Zentralklinik, Bad Berka, Germany*

Dr Sutcliffe:

I would like to go to Head and Neck cancer, Helen you will have to help me I didn't quite get them down as quickly, it seem to me that cervical neck nodes, with suspected carcinoma of unknown primary, you are putting forward as a recommendation for PET studies. ...Sorry, the appropriateness of that recommendation? I believe in the initial staging of disease you did not believe that PET should be recommended.

Dr Anderson:

I said with selected patients where it could potentially affect treatment planning there was a role for that - selected patients.

Dr Sutcliffe:

So it is a highly individualized type of recommendation? Ok and the diagnosis of suspected recurrence after 3 months of radiation.

Dr Anderson:

Yes, I thought there was a role for the detection of recurrent disease. In a situation where there is some doubt as to whether it is post surgical scarring or post radiation changes and perhaps disease is expected there definitely is a role.

Dr Sutcliffe:

Comments on that either from the floor or from our expert panel? Would you accept those indications; would you say there are some that are not there that you believe to be important?

Dr Conti:

I think the one area that I believe is significant is the patient that presents with advanced disease and you are still considering radical neck resection. It is that group of patients, there is a very high incidence of conjulateral disease and it can have a direct impact on quality of life, morbidity for the patient, it may not affect outcome in the end, but I think it is up to 30 % of conjulateral disease that it is undetected by anatomical imaging in that group.

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Dr Wahl:

And I might also comment that certainly Peter Valk has described this and we certainly have seen this anecdotally when you see the patients with more advanced primary disease can uncommonly have disseminated disease, not uncommon thoracic metastasis which would preclude the radical neck surgery so may be that would be one of the groups you might consider doing selected studies pre-surgically but I would also do more than just the neck. I would certainly do the whole body study. With evidence at least anecdotally being most for thoracic and upper mediastinum of abnormalities.

Dr Baum:

Also and not forgetting the secondary tumours, which are present in up to 15 to 20% of these patients like esophageal and chin cancer and lung cancer I mean the toxic substances are the same.

Floor:

I think the discussion on Head and Neck cancer needs to be a little less generic in the case of nasopharyngeal cancer which is a disease that obviously is much more common in Asia and other parts of the world, we also see a lot of it in Vancouver, where the incidence of metastatic disease at presentation is very much higher. Maybe, I haven't heard it mentioned, it is I think quite a distinct entity and different both epidemiologically and pathologically than Head and Neck cancer due to alcohol and tobacco use.

Dr Sutcliffe:

Any comments from the Panel with respect to distinguishing nasopharyngeal as a specific consideration?

Dr Conti:

We have studied a number of cases like that, you are absolutely correct when you see really frequently metastatic disease beyond the Head and neck region in that population - and it goes back to the comment I made earlier. That if you ask the question whether there is metastatic disease you need to use the test that best demonstrates the metastatic disease if you are going to act on the results. So in this particular case once again you have a choice perhaps between say CT and PET, I think that PET has a distinct advantage as you have heard throughout the day.

Floor:

I just wanted make a general comment, it seems to me that in the discussion for the lymph node we do see that when you use the definitive gold standard of biopsy that in fact often it is actually low and the problem is in a lot of the studies where you are looking at higher stage disease, metastatic disease, that in fact the gold standard, I am not quite sure what was in these studies. So the sensitivities and specificities that you are quoting that you are suddenly going to apply to a group of patients, primarily staged in which you plan to substitute this wonderful test isn't clear to me that those are the numbers that you would chose to use, so that I am not sure that you can take information that is being applied by sequential layering of a multitude of tests to suddenly say that this one test is going to be the definitive metastatic search is actually fair or correct and that I think that it does beg determining the true incidence of the true specificity and sensitivity in a completely different setting, than some of these tests studies that have

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Floor (cont.):

been quoted so the gold standard has been really unclear for some of these that we have been discussing?

Dr Shreve:

If I could just comment, obviously the gold standard is tissue, if you can get it and even tissue gold standard isn't always 100% because there can be sampling errors in biopsies. This is a problem with many of these studies is what is the gold standard in determining sensitivity and specificity and we have struggled with that over the years because in many instances every single metastasis is not actually proven so if you count lesions usually you don't have tissue proof of all the lesions but the theme we keep coming back to is, if you ask the question: is there metastatic disease and you want to do an imaging test. Then the question is which imaging test is most accurate for metastatic disease and there is a preponderance of evidence that that is PET.

Now typically when we find a distant lesion we will get tissue proof and I think it has also been reiterated here that in the neck and mediastinum, you really need to prove by tissue diagnosis if you can, whether something is indeed a positive node because of the false positive rate due to inflammation but it is not that we completely substitute PET for tissue diagnosis. We use PET to direct us to most efficaciously to the correct tissue diagnosis and relative to CT, PET has clear cut advantages in most of these neoplasms.

Floor:

I just want to go back to colorectal, for a minute, the one recommendation that it be used in patients who are asymptomatic but have an elevation of their tumour marker there have been a number of studies published showing that there isn't any really definite benefit to following patients with tumour markers and it was my understanding that we are trying to educate the mostly community physicians to stop ordering CEA's, stop ordering CA15.3's, 19-9's in patients who have been treated for their disease. So I am just wondering how that recommendation ties in with that because I mean I certainly have been in that situation before where I have had consults coming in from family doctors that someone who had a breast cancer or colon cancer resected a few years ago and now their marker is going up and they end up with a million dollar work up and you don't find any thing.

Dr Baum:

I think that one of the main reasons to doubt about the usefulness of tumour markers was the lead-time of tumour markers because conventional imaging was not able to find and localize the tumour. Now I think this has exactly changed by application of FDG-PET at least in colorectal cancer, in our series and this involved several hundred patients there was if I remember only two patients with an elevated CEA where the PET scan was negative and this turned out to be brain metastasis of colorectal cancer which is quite rare, but where we missed it, but all the others had positive lesions so in my view it is very important to do tumour markers in the follow up of high risk patients especially Dukes C and so on, and to detect early disease especially single liver metastasis, which can be resected or single lung metastasis which can be seen and resected.

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Lung Cancer

Speakers:

- ❖ *Dr Ken Evans MD: Thoracic Surgery Vancouver General Hospital*
- ❖ *Dr Simon Sutcliffe: CEO, BC Cancer Agency*
- ❖ *Dr Peter Conti, MD: Associate Professor of Radiology, Clinical Pharmacy and Biomedical Engineering USC*
- ❖ *Dr Paul Shreve, MD: Assistant Professor, Internal Medicine, University of Michigan Medical Centre.*
- ❖ *Dr Richard Wahl, MD: Director of Nuclear Medicine, John Hopkins University*
- ❖ *Dr, Dr Richard Baum PhD: Chairman PET Centre, Zentralklinik, Bad Berka, Germany*
- ❖ *Dr Edward Coleman: Professor of Radiology, Duke Medical Centre*

Dr Evans:

So in summary, Simon here are the indications I think we should be using PET scanning in thoracic malignancy:

1. I think we should be using it routinely in the staging work up for carcinoma of the lung and getting back to the earlier presentation.
2. I think that we should be using it routinely in the staging work up for carcinoma of the esophagus in patients who are going to undergo surgery for radical treatment.
3. I think it is important in evaluating indeterminate pulmonary nodules as Dr Baum mentioned, and finally
4. I think that it is indicated in patients with thoracic malignancy looking for recurrent disease.

Dr Sutcliffe:

Lets go straight to the discussion of these indications and both yourself and Dr Baum put forward the evaluation of solitary or indeterminate Pulmonary Nodule. Can we now state that this now is state of the art practice, that it is the definitive investigation for the solitary pulmonary nodule?

Dr Coleman:

I certainly think that it is an important study in the evaluation of the indeterminate nodule, Dr Evans asked well what do you do if the PET scan is negative, and I think that we still need to follow these nodules because the sensitivity in PET is not 100% it is 95-97% sensitive so if the patient has an indeterminate nodule then one does need to follow this at 3 month intervals with a CT scan and that certainly is true if it is not amebolic as Dr Baum showed some cases. If it is amebolic my guess is the chances of that is zero but we don't know that. So I think that these indeterminate nodules – you still need to follow, it is a small percentage, but you do need to follow them. Dr Evans mentioned that one of his cases was a bronchiole alveolus cell cancer – PET has a sensitivity of probably around 50 to 60 % in bronchiole alveolus cell cancers and carcinoid tumours those are the two cell types where it is less accurate.

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Dr Coleman (cont.):

Another observation is that we have been talking about non small cell lung cancer – that is where all the data is in the literature but those of us who do many PET scans are doing them for small cell lung cancer – it is elegant, it is extremely sensitive for detecting small cell lung cancer. The situation there is different than in non small cell lung cancer – limited verses extensive disease following therapy and I think that we will see the data expanded into small cell lung cancer in the future but for right now the data is on non small cell lung cancer.

Dr Shreve:

I think there is one point to make about lung nodules is, to say that PET is the definitive test is probably not the most accurate way to put it – it is one of the important tests, but it depends on the patient and the patient’s history, and the location and size of the nodule. Many times a large mass in a smoker where you pretest probability of cancer is probably 90% or better you are really going for histology as far as evaluating the mass. If you are doing a PET scan it is more for staging, than really evaluating a nodule that is almost certainly cancer so many of these patients present to us, and we are a referral centre, and that may have something to do with it, they present, already having a tissue diagnosis or at least one attempt at tissue diagnosis. So you have to look at PET in the context of the individual patient’s presentation. In some cases nodules are hard to biopsy because of peripheral or near the apex or in the diaphragm and then again PET would be probably be the definitive initial test to do but it all depends on the patient at presentation.

Dr Baum:

Just one small comment. As I mentioned I think it is very important to do an interdisciplinary decision, it is not a decision by one modality or one clinical specialty, you really have to include your pulmonologist, thoracic surgeon, I mean it is quite different from patient to patient if you have a 75 year old with a lot of risk factors it is much different from a 35 year old with no risk factors and probably in the last case we would more often be surgically aggressive, whereas in the other case we would be more conservative, so it is very important to for all.

Floor:

Ken presented one case with an esophageal and a non small cell but what safeguards are there for multiple lung primaries for although it is not common, certainly we see patients that present with multiple lung primaries and one of the concerns could be that PET would overcall those as metastases?

Dr Coleman:

Well certainly that is the case we can’t differentiate multiple simultaneous primaries from a metastatic lesion, but if we have a patient that does have two separate lesions, our surgeons will biopsy each, and not infrequently there will be the squamous cell and adeno that they are different, so depending on the situation and that is what Dr Baum was mentioning, you have to take the patient into consideration and look at all the information you have but simultaneous primaries do occur and just because we see lesions in opposite lungs does not necessarily mean that it is metastatic disease if we have a lesion, in both lungs and one in the adrenal and one bone then you have your answer but if you have just two focal lesions, simultaneous primaries certainly has to be considered .

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Dr Lam:

I would like to ask the panel if we have a negative PET scan, can we bypass a mediastinoscopy for staging prior to operation?

Dr Baum:

For my perspective, yes if you compare the results by mediastinoscopy and by PET, it is clear-cut that PET is more sensitive than mediastinoscopy; I mean this is especially true for the left side for super aortic and para-esophageal lymph nodes and so you can hardly reach with mediastinoscopy, so if the PET scan is negative you can leave out the mediastinoscopy.

Dr Coleman:

At our institutions most of the patients will still undergo mediastinoscopy – T1 lesions may not, if there is no evidence of adenopathy on the CT scan, but still most patients do undergo mediastinoscopy even following the PET scan T1 lesions with a negative PET may not.

Dr Conti:

Our experience at USC is similar – most of those cases will go to mediastinoscopy, however I just want to mention a caveat; some cases where you have a hyper metabolic pulmonary lesion, and you may see mild uptake in the hilum mediastinum your tendency perhaps is to consider that as inflammatory process either because it doesn't look similar to the primary tumour or because the pattern based on other ancillary findings suggest that it might be inflammatory, in several of those types of cases end up being metastatic disease and usually because it is very minimal the amount of tumour burden not necessary giving you the same presentation of level of activity that you might see in the primary so in those types of situations we usually take those patients to mediastinoscopy almost as a routine

Dr Evans:

I think Steve, that for any thing other than a T1 lesion that needs to be studied further with PET and mediastin oscopy

Dr Lam:

A question for Dr Baum please, one of your slides showed that PET was not useful for staging metastatic disease in the brain, could you clarify that a bit further especially if you suspecting or only expecting a solitary lesion – does it make a difference if it is only a single metastases in the brain? Is PET accurate enough to determine that?

Dr Baum:

No, I don't think that PET is useful in any way to look at brain metastases because sensitivity is just not high enough. So if you have a single lesion detected by MRI or multiple lesions it depends; usually it is not operated on in small cell lung cancer.

Dr Coleman:

The problem with PET in the brain is the normal cortical uptake and seeing small metastases at the grey white junction, we just do not see. There have been several studies including one from Duke University that maybe 10-20 % of patients that have brain metastases will you detect so it is a very small percentage that you do detect so most

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centres do not even include the brain as part of the whole body study because the sensitivity is so low.

Dr Sutcliffe:

I am just going to go to another indication that would seem to be that in medically fit patients with non-small cell lung cancer, you have indicated for lymph node staging and also for exclusion of distant metastasis i.e. defining the operable patient cure – Would you comment on that in the context of is that the state of the art statement now, is that where the practice is?

Dr Baum:

I can comment from our centre, which has PET and I would fully agree on what you said for our Centre and I think for most of the centres collaborating with institutions having PET, having PET themselves. So for Germany yes. This is I think state of the Art. Unfortunately about 60% of the patients are not operated in centres so in smaller hospitals or peripheral Hospitals and in these institutions very often there is PET it is not available. So one must differentiate between what is really state of the art and what is clinical practice. I think that many of the patients still do not receive PET scanning in Germany before a lung operation.

Dr Coleman:

Absolutely the primary value or one of the major values of PET is the staging of M disease, do these patients have distal metastatic disease?? And PET has shown to be very accurate, more accurate than CT or bone scanning in detecting that – it certainly is the staging procedure of choice.

Dr Sutcliffe:

Could you comment on detection of recurrence which Dr Baum you had indicated as one of your 1A recommendations in terms of putting that forward as an indication. Is that an across the board statement or is there any sub-distinction within that as to the use of PET?

Dr Baum:

It is done mostly after an anatomic test such as CT which shows some alterations, which are not clear cut related to recurrence so in this situations yes, I think is a very good method. It has a very, very high sensitivity, coming from all studies that we looked at, and it is also very important for making the therapeutic decision as to what to do on a

Dr Baum (cont.):

patient. Some patients you can still do local radiation therapy, if there are distant metastases, in addition to the recurrence, you probably better with chemo therapy and radiation therapy in some areas so it is very important for making the therapeutic management correctly using of PET in the recurrent situation.

Dr Sutcliffe:

Presumably most specifically, when you consider patients for the surgery option?

Dr Baum:

Yes absolutely all the tests show that it also has a very high specificity especially in patients that have not been irradiated before

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Dr Sutcliffe: Any further comments from the floor for lung indications for PET? Yes.

Floor:

I have a 2 part question actually – the first part pertains to image acquisition for radiotherapy planning and the second is about the coincidence option on gamma cameras For radiotherapy planning is it your routine practice to acquire your PET scans in the treatment position? – I notice that for most of the images that you presented the arms were down and presumably the treatment position we would have the arms raised – Ideally the CT and PET images would be acquired at the same visit, with the combined machine for that purpose, in treatment position but failing that for your routine initial staging would it be therapy planning and the second part of the question: For PET detection is there anything that is lost when you compare the dedicated PET?

Dr Baum:

Maybe for the first part I would like to answer - Nothing is routine up to now for radiation planning therapy it is very much in academic environment and we are really looking and testing a lot of different approaches to see what is the best for image fusion. What you have to keep in mind and one is of course the position of the patient and I mentioned the breathing is very important and we now have software available that runs on a nuclear diagnostics workstation where you can very nicely by software interpolate the images and do the image fusion process so these things like arms up and down is not so much important if you are using clearly for the purpose of radiation therapy. Planning should of course be as much similarity between the two studies as possible. The second question I would like to pass on to Dr Coleman.

Dr Coleman:

Yes I agree with Professor Baum concerning if you are going to be doing these studies for primarily radiation therapy you may want to use the same bed, curve bed, flat bed, you may want to use the cradle arm or the head down what ever is going to be done for therapy planning that certainly would facilitate the fusion and making sure that the therapy volumes were appropriate. Concerning camera based PET vs. Dedicated PET for therapy planning – you are going to have more accurate localization of the FDG with the dedicated scanner when they are compared to the camera based PET. With the camera based PET you can detect lesions you cannot detect as small a lesion as you can with the dedicated PET scanner that is the camera based PET will not detect the small lesions as will the dedicated scanner and further more the edges are going to be blurrier with the camera based PET than with the dedicated PET – you will have more accurate localization because of the higher resolution with the dedicated PET compared to the camera based PET.

Dr Wahl:

One further caveat with the camera based PET methods. If you don't use attenuation correction with the coincidence option then you will also have anatomic distortions which can make matching the shape of the thorax difficult so I think that most of the efforts with treatment planning have focused on dedicated PET where the body outlines are preserved with the same geometric ratios. Without attenuation correction the tumours can be distorted often lengthened in

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the anterior posterior dimension and as I have said the edges blurred, in some cases cerebral lesions can look a little like cigars so there are really some cautions in addition to the difficulty in seeing the smaller lesions with a coincidence system – especially with the earlier ones that were on the market.

Dr Conti:

One other comment that I would also like to make is that as a result of this meeting to day you are going to be flooded with referrals for PET scans of course and the throughput from the coincidence cameras is significantly slower than the dedicated PET.

Lymphoma

Speakers:

- ❖ *Dr Joe Connors MD: Medical Oncology, Vancouver Cancer Centre*
- ❖ *Dr Simon Sutcliffe: CEO, BC Cancer Agency*
- ❖ *Dr Peter Conti, MD: Associate Professor of Radiology, Clinical Pharmacy and Biomedical Engineering USC*
- ❖ *Dr Richard Wahl, MD: Director of Nuclear Medicine, John Hopkins University*
- ❖ *Dr, Dr Richard Baum PhD: Chairman PET Centre, Zentralklinik, Bad Berka, Germany*
- ❖ *Dr Edward Coleman, Professor of Radiology, Duke Medical Centre*

Dr Connors:

Just quickly to re-summarize what I was proposing is that we would use PET scanning in two I think fairly well described situations:

- The staging indication would be in specifically patients with early staging disease, with aggressive histology lymphoma, where our treatment plan is brief chemotherapy and radiation and where realization of more advanced disease would lead to an extended course of chemotherapy - so a major treatment change. We would not be using it for the indolent lymphomas or Hodgkin's lymphoma for two different reasons:
 1. We need more information about which indolent lymphomas might have accurate uptake, and
 2. In Hodgkin's lymphoma, our success rate is high enough that we don't need an additional staging test.
- For advanced disease the crucial issue is discerning the identity of residual masses and here one could say instead of what I have said before where I said at advance disease post treatment evaluation to add radiation, it could be add any additional treatment. If we had sufficient confidence in the test, we might for instance add high dose chemotherapy and stem cell transplantation if we in fact quite strongly believe to the positive predictive value, but any rate, the simplest situation to understand is the addition of radiation and we would use it to evaluate residual masses. A patient in complete remission by CT scanning then wouldn't fall into this category where the overall yield seems to be too low to justify routine PET scanning for that population. For advance disease where we planned radiation but we are concerned that it may confer undue toxicity we would use PET scanning to eliminate the use of the radiation in those patients where PET scanning is negative and you saw from Dr Voss's results that that is actually the use to which we have most frequently put PET scanning to use so far and then.
- Finally, in highly selected patients where potentially the patient has relapsed and the other tests we have available are not yielding an unequivocal answer we would use PET scanning to help to understand the whole situation.

So those are the indications.

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Dr Sutcliffe:

Thanks very much, could I perhaps pose those to our expert panel for comment?

Dr Wahl:

I would just comment that in the low grade lymphomas one of the papers that you refer to looking at the mucosa associated lymphoid tumours or lymphomatized tumours – those were mainly gastric I think in that paper for 10 of them, those are small volume tumours. I think that it is pretty clear that PET is not indicated in that kind of tumour especially in the stomach because the background uptake is fairly high. I think that most other studies though, when you look at larger volume, even lower grade lymphomas, several you didn't reference have shown reasonably high sensitivities of FDG. In those tumours you will have a higher incidence of false negativity but I'm not quite as pessimistic as you. I think the ones you selected, the ones particularly in the stomach are a particularly bad performing group partly because of the low volume so when we had looked at lower grade lymphomas we had fairly high success rate and certainly with gallium I believe they are more commonly negative, so I would agree with you that these lower grade lymphomas may not be well imaged but we have had abundant cases particularly cases we treated. With radioimmuno-therapy when the FDG uptake has been intense and I think the real issue is how is it going to change your management of those? So I'm not as pessimistic about the low grade lymphomas as you were from the data that you selected.

The data on bone marrow involvement, 16% of your patients had additional sites of bone marrow involvement identified which you thought was not significant, there was another paper from Ohm, Germany I think that showed about 20% may be higher incidence of finding bone marrow lesions by PET when the bone marrow biopsy was negative so this is for 1 in 4 or 1 in 5 patients and that just depends on how the treatment is going to change, but if you think that bone marrow biopsy is important for staging the marrow then the fact that you find 1 in 4 or 1 in 5 additional patients with PET might be important depending on how treatment is changed.

Again, I thought that you may be being more conservative than I would have been in terms of indications in the lower grade patients other than that the cure rates of 97% are pretty important but my sense from our oncologists and radiation oncologists is that there is a little bit of a tendency to move to less chemo therapy in some of the Hodgkin's lymphomas because of the higher incidence of side effects down the line years later for patients that have had both chemo and radiation and may be the radiation for cure is still not such a bad thing to look at. I know that this has been there are different groups who have different view points but my sense right now is that, having seen several cases of failure just outside of the radiation field, that if somebody is thought to be curable with radiation therapy alone then doing an initial PET may be quite a reasonable thing to do to define that field because it is your one chance, it is your best chance for cure. It is hard to match fields afterwards so I think as least there is some opinion in the US that trying to plan those fields for initial curative radiation therapy is really where PET can make a big difference if you find a little bit more extended tumour so those are just some comments – I generally agree with you.

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Dr Connors:

You are correct we have to put these things in the local context. We don't manage any patients with Hodgkin's disease with radiation therapy alone in all patients receive some systemic chemo therapy and it is in that context that I didn't think it would add to our usefulness. With regard to the indolent lymphomas, that also has to be placed in context because 90% of these patients with advance disease as defined by other modalities of investigation. So it would still be a rather small and confined group where one would have to think through particularly what the consequences of missing the advanced disease which would then only be discovered when they relapse after some rather well tolerated field of radiation so I did try to err on the side of being quite conservative here so that any indications that we do come up with are highly defensible. Thanks for your comments.

Dr Coleman:

Yes, I agree with the comments that have been made. I think that you are being conservative in its utilization and certainly there is nothing wrong with that to start out. Get experience. I do strongly recommend that FDG-PET replace gallium, I think that for those of us who have been doing Gallium scans for years, just the quality of the information, the accuracy of the information is just much better with the FDG-PET than with gallium so if nothing else for those patients who now have been getting gallium scans, they should be getting FDG-PET scans then the information will be much better.

Dr Baum:

Just a small remark concerning gallium. I think one should also mention the radiation burn for the patient: comparing gallium with FDG-PET, especially in young patients was longer follow up period and repeated scans, it comes to an essential amount of radiation from gallium, If you use 5 MC per dose it is some 4 to 5 folds the radiation exposure as compared to F18 FDG-PET.

Dr Conti:

Just in our own clinical experience in Los Angeles, I think the issue of lymphoma and advanced disease needs to be perhaps be reconsidered in the sense that looking at disease even if it is advanced at the time of diagnosis as a baseline for level of measurement and our understanding of the metabolic presentation of the cancer, because when you go back and evaluate residual disease these cancers do vary even within cell type in their intensity of uptake. So in our experience it is usually very useful to have that prior study to refer back to, as opposed to deciding not to do the PET scan and then being considered down the road for whether or not there is residual disease - you have no base line at that point.

Dr Connors:

I agree and I think as we gain more experience that that might well be another way that we would use PET scanning and also worth commenting about the ability to distinguish the different histological types at presentation because a substantial fraction of patients who appear to have indolent or low grade disease on presentation actually harbour islands of transformed disease. I myself would be particularly curious as a research question as to whether PET scan positivity in diagnosis for indolent lymphomas might not actually predict for such islands of more aggressive disease, something that we will be able to find out in the future.

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Floor:

Joe I just wanted to ask in reference to the second and third point – both of these would be CT positive patients that you had referred to in both in our group and in the literature, there was one group that had 5 negative PETs; I mean they were all negative PET – positive CT and negative PET and 19 of them, of these 5 had an unpleasant outcome I don't remember if they relapsed or died or something. That is a fairly high rate of bad outcome for that group that you would not be offering them treatment. Do you remember that slide and I just wonder at what level of false negative that you would be willing to accept for this group when most of them presumably would be eligible for a localized treatment plan in addition to their chemo? The 25% relapse, I do not know right there does that not make you nervous or what you would do about that. I presume you would not have offered these people additional localized therapy and is that enough level of comfort?

Dr Connors:

First of all the recommendation that I am making is that we undertake to do a PET scan in this situation because the patient has a positive PET scan so that is evidence of residual disease at the end of their treatment. Whether we would be willing to rely on the negative PET scan is a good question – this study had the lowest negative predicted value out of any of the studies reviewed and I'd want to put all of the studies together – rather than basing my conclusions on a single one. Remember that in lymphomas we do have back up treatment and so experiencing a relapse may not have some of the implications that it would in a solid tumour especially these patients that were patients with Hodgkin's lymphoma they would still have a 60 or 70% chance of being cured with back up treatment and so it may make good sense especially if this figure is more like the 5% to 10% that has been found in the studies with a larger number of patients. To observe these patients for the minority that relapse, embark on more intensive treatment at that time. Because we would not be offering additional treatment, and this would be the group that we would learn about most quickly and we would find out if in fact this was an error in decision-making and realise that and could revise our treatment approaches after that.

Dr Wahl:

Just a comment the other issue and this particular paper there, the number of instances of CT negative, PET positive was very low in this study, but there was an article in the JCO in January of this year (2001) where if I recall correctly there were something like a 15% - 20% incidence of PET positive, CT negative cases. Which was higher than most studies, but in that particular study those cases which were CT negative, PET positive had a very early frequency of relapse and I have a slide and will show you that later, so obviously neither a negative PET nor a negative CT are completely indicative of good long term survival – I think both can miss low tumour burden due to the physics of the detection of the method, so your negative studies will – you are not going to find a 3mm focus lymphoma in general I would think, especially if it has been metabolically stung by chemo therapy. So these aren't like an in vivo PCR of the whole body, so I think it is fair to say that negative or both are not necessarily going to carry a negative predictive value, but this is particularly bad, this is worse than the average study as was pointed out, with a quarter progressing.

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Dr Sutcliffe:

It would seem then that the indications that have been put up are:

- a) Recognised within the context of our own local management plans
- b) Would be recognised as being conservative relative to the evidence but supportable by the evidence that is available in the literature and practise.

It would seem a fairly strong recommendation that if you have PET capability, there is no reason to be doing Gallium scans in lymphoma any more and just as I am allowed the prerogative it raises the interesting question at some time from a health system perspective whether staging of lymphoma would go over to PET based evaluation and one would in fact reduce the frequency in which one is doing other types of investigations, the argument I image would be weak at moment from an economic perspective but that could presumably change over time and acceptance by the profession.

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Melanoma

Speakers:

- ❖ *Dr Amanda Jones, Medical Oncology, Vancouver Cancer Centre*
- ❖ *Dr Simon Sutcliffe: CEO, BC Cancer Agency*
- ❖ *Dr Peter Conti, MD: Associate Professor of Radiology, Clinical Pharmacy and Biomedical Engineering USC*
- ❖ *Dr Paul Shreve, MD: Assistant Professor, Internal Medicine, University of Michigan Medical Centre.*
- ❖ *Dr Richard Wahl, MD: Director of Nuclear Medicine, John Hopkins University*
- ❖ *Dr, Dr Richard Baum PhD: Chairman PET Centre, Zentralklinik, Bad Berka, Germany*

Dr Jones: *(Part of main presentation)*

So in summary in terms of recommendations PET is not sufficiently sensitive certainly compared to Sentinel Node Biopsy to evaluate Stage 1 and II and patients and distant metastasis in this group of patients are very rare so I think it will not be very cost effective to screen this group. PET is useful in evaluating palpable nodes in Stage III patients and may detect, may direct therapy in this group if radical surgery is contemplated. In Stage IV patients, PET is useful in the preoperative assessment of patients for whom a potentially curative surgery with metastectomy is planned. It appears to be more sensitive in Stage IV patients in detecting intra abdominal disease and bony metastases and it does not apparently have any role in the evaluation of primary unknown melanoma.

Dr Sutcliffe:

Thank you very much Amanda, we are going to open this up for discussion now. Dr Baum do you have a comment?

Dr Conti:

Perhaps while he is setting up I can answer a question or make a comment actually. I just want to make sure that we all understand that there are some issues related to measurement for efficacy of PET in terms of what its role should be. I think it is important to distinguish outcomes from management change. Outcomes are highly dependant on the available therapy and as imagers we may or may not have a significant impact on outcome as it relates to treatment, on the other hand if a decision is made in terms of whether or not to treat or whether not to treat with a different modality the original one that one was originally considering you get into an issue of management change or to give additional chemotherapy or things of that nature – that is probably a more reasonable yardstick, compared to measurement of health outcomes.

Dr Sutcliffe: Thank you. Yes Richard.

Dr Baum:

May be just a short comment on this paper by Mijnhout in Cancer, which I really do not understand, also about the conclusions you draw. We have all the publish in cancer, we

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Dr Baum (cont.):

should exactly know, in '98 a prospective study and without being too long I just want to would like to present the data here that where primary staging in high risk melanoma so I agree there is no role in Stage I and II because the frequency of metastasis is just too low but as you know in Stage III, the prognosis is deteriorating dramatically. We have done it also for restaging for patients with suspected or proved recurrence for deciding as you also mentioned if there should be surgery or not. We have compared that and these were 100 prospective, consecutively studied patients with blinded evaluation of the data, that was at my time at the University of Frankfurt, and we have done this standard battery of tests and compared it to one whole body PET, 52 were in the group of primary staging and 48 were in a group for restaging. This is just one example with a hypermetabolic lymph node in the groin which was unclear and this are our results and I think this will be confirmed in many studies, especially from Switzerland I might say from Zurich there are some prospective studies which were also not mentioned by this guy Mijnhout and we have had a sensitivity, also we gave patients and single lesions so there is a direct comparison, exactly in Cancer published with a 100% sensitivity in the group of the patients for primary staging and for metastasis was 91.8 and with a very good specificity also which is much better than the conventional imaging and just another example here which shows a lesion which we thought would be in the spleen or just above the spleen and when you do image fusion with the CT scan you see it is just below the diaphragm outside the spleen and it was removed and was a 1.2cm lesion so in melanoma I think there is a role in Clark level III, IV, for staging high risk patients and also for restaging patients to decide before therapy. So I don't understand this paper you make citation of?

Dr Sutcliffe: Thank you very much. Do you want to respond to that now Amanda?

Dr Jones:

One of the things that came out from the Mijnhout review, and also I did look at your paper in Cancer as well, was it became very difficult to actually determine which patients were, in which patients metastasis were detected when those patients were clinically Stage I & II and which ones where metastasis were detected where there was a very high pre-test probability because there was suspicion, because of radiological abnormalities or symptoms, where these metastasis were being found and I found that very difficult to get out of your paper, how many of Stage I & II patients who were asymptomatic actually had metastatic disease found at diagnosis, the second.

Dr Baum: Can I answer to this question?

Dr Jones: Sure.

Dr Baum:

Possibly you didn't read it correctly, because it is clearly written that the inclusion criteria were Stage III patients. We didn't look at Stage I&II, I mean the reason for that was that as you know the 5 to 10 years survival rates are quite good and there are not frankly many metastasis so we decided to go directly in the higher groups in Stage III.

Dr Jones:

No. I think that we are talking about different things: you are talking about T stage and I am talking about clinical stage.

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Dr Baum: Ok, I am talking about Clark level.

Dr Jones: Yes, I am talking about Clinical Stage I & II patients.

Dr Baum: Ok.

Dr Jones:

As opposed to Clark’s levels, which we do not use any more, we use millimetres of depth of invasion.

Dr Baum: Yes, we too.

Dr Jones:

So I think there is no question that it is of value in the analysis of patients at Stage III, Clinical Stage III, and that is patients presenting with palpable nodes, but in the two series, in which patients, a large series including 50 to 100 patients where systematically PET scanning has been compared with Sentinel Lymph Node Biopsy the sensitivity for detecting disease within the regional lymph nodes is very low.

Dr Baum:

Actually, we were not interested in the regional lymph nodes because this is done also in our Centre by Sentinel Node and it is very clear that PET cannot detect microscopic disease and in some patients you even have to use PCR to detect it, and I think this is not, this is not the role of PET. But from a practical point of view, I mean to have a stage, a clinical stage what you are speaking about you first have to do the evaluation of the patient. So our starting point was one step earlier, I mean after resection of the primary tumour, you look at the tumour thickness right? and you clearly can say if this is more than 1.5mm the risk increases and this is Clark level III so our decision way was: If this is Clark Level III or higher then it is a high risk patient, and then lets do a PET scan verses a conventional battery of tests, and it came out that PET is much better than conventional staging methods, especially concerning specificity, I mean if you look at our data, this group the specificity was really lousy, if I remember right it was 48% or something for conventional staging with a lot of false positives, and I think this is another argument to use PET in this group.

Dr Sutcliffe: I’m just going to bring Dr Wahl on in that discussion.

Dr Wahl:

Well, I’ll confess, I didn’t read the paper in Cancer 2001, I didn’t see it yet, but I did have a role in writing the first paper in which PET was describing melanoma in 1993 and found that it worked pretty well and also worked in animals before that, and I think one paper that wasn’t referenced in that review article, I believe. If I can remember who published it was a McFarlane and was that referenced in their paper? I think if I recall correctly almost all those patients went to surgery there weren’t a lot under about 20 this was in the Journal of Clinical Oncology and in that study the sensitivity in PET was superior to that described in the paper from Indiana but I think it is quite clear that our patient population included more patients who had palpably abnormal nodes and in that group PET does really well, but I think it is absolutely clear that you will fail to detect small lesion volume melanomas with PET and that it is not comparable to Sentinel Node

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Dr Wahl (cont.):

for sensitivity and there has been a pretty good article from Italy, showing that the detection capability is dependent on the size of lesions, it observes a 1cm - 100%, even with an older scanner, and you get down to 3 mm and you may be at the 30% level, so it is clearly size related. So I would agree with you on suggesting that it would be more appropriate in larger tumours and in more advanced disease. I do think though that the assessments based on the number of lesions are quite as important, maybe less so for melanoma but in a lot of times, you know whether it is 5 verses 10 makes no difference but the issue, zero verses one, is really quite important and in colorectal which was discussed earlier the number of lesions in the liver can make a big difference as to resectability. So my general attitude is if you want to use a diagnostic test, then ask whether somebody has metastatic disease you should use the more sensitive one that if you don't want to know whether they have metastatic disease you are probably better off not ordering a test.

Dr Sutcliffe: I am going to stay with.

Dr Wahl:

I am sorry just one other point, I am very sorry, but the specificity described in the paper of some 47% from Duke University if I recall correctly that was high sensitivity low specificity, in a fairly large study. Some of those specificity figures are misleadingly low because they don't include a physical examination of the patient, I think that the studies from Zurich, and our work have shown that inflammatory lesions of the skin, surgical incisions, boils and things like this can cause false positives and it really is important not to just look at a scan but to correlate the scan results with clinical findings because otherwise you can end up with lower specificities with cutaneous lesions just misleading you completely, that could be confused with melanoma, so I think the clinical exam even with our scanners is still going to be important for cutaneous abnormalities. So I think that may in part be the cause for the lower specificities as has been reported in some studies.

Dr Jones:

I think the main problem is the studies have very heterogeneous groups of patients and they have Stage I, Stage II, Stage III, Stage IV and overall they may have high sensitivities and specificities but it seems to be that mostly that's detection of metastatic lesions in advanced stage patients so I would make a case that for Clinical Stage III and clinical Stage IV patients, PET scan is very relevant, that the melanoma has a very high uptake of FDG, higher than a lot of other tumours, and it has very unusual patterns of metastatic spread and therefore PET scan will often direct you to areas that you would never envisage were going to be affected by metastasis, but I am simply arguing that compared to Sentinel Node Biopsy in early stage patients that it is very insensitive and in early stage patients with respect to detection of metastatic disease at other sites, metastatic disease at other sites is very uncommon in patients in early stages without, you know even taking patients with deeper tumours, metastatic disease at presentation is very uncommon and so it is probably not that cost effective and the specificity seems to be lower in these early stage patients because you pick up a lot of abnormalities that don't turn out to be related to metastatic melanoma.

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Dr Sutcliffe:

So Amanda it seems to me that your recommendations would be:

1. The evaluation of nodes in patients with Clinical Stage III disease where surgery is considered an option.
2. Patients with Stage IV disease where isolated metastasis would yield surgery as a treatment option.

Dr Jones: Yes.

Dr Sutcliffe: Those are the two options that you are coming forward on.

Dr Jones:

And I think thirdly in evaluation on patients presenting with bony pain or with abdominal symptoms, or undiagnosed GI blood loss, where I think PET is useful and is more sensitive than all other investigations including probably endoscopy in establishing the site of metastatic disease.

Dr Sutcliffe:

Having heard those recommendations is there anybody from our guest faculty who feels those would not be appropriate indications for PET? They may be conservative relative to our discussion but.

Dr Baum:

No I agree, nearly completely but I would really ask to take the story one step before the staging, before you get the stage, you have to do the whole body staging and I would include in the staging process of patients with high risk melanoma, that means with a tumour depth/thickness of more than 1.5mm, I would include today PET, because as our series showed you have, I don't agree on that with you completely. You have in a certain number of patients who have distant metastasis detected also in the primary staging but which are not detected by other methods. So this high risk group I would include PET in the staging algorithm.

Dr Sutcliffe:

On depth of invasion as a test for selecting PET in staging - Peter, do you have a comment?

Dr Conti:

I think, I agree 100%, with Dr Baum here, I think if you have a situation where you have a certain probability of metastatic disease based on lesion depth. If you ask the question, what is the stage of the patient, and you are going to trigger a series of steps that is going to assess the stage. The best test that is available today is PET, period.

Dr Shreve:

I would, just to make that more succinct if you are considering a head to toe CT scan, PET is the superior test compared to a head to toe CT scan, even with thin cuts, and there was something said earlier that CT of the liver was more sensitive than PET for melanoma of the liver, that is just absurd. That is just totally absurd. It might be more sensitive yet the specificity is practically zero because if you call every too small a characterized lesion of the liver which for those of us who are radiologists are just as common as anything, and you say those are all metastases without actually proving them

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with biopsy, then may be it is more sensitive, but there is no way that I can see how CT is going to be more sensitive than PET for metastases to the liver and I would ask my colleagues if they see how.

Dr Jones:

What I actually said was that it was more sensitive with respect to the numbers of lesions that is all.

Dr Shreve: CT is finding more lesions than PET?

Dr Jones: Yes. Not on a per patient basis

Dr Shreve: No but I mean in the liver.

Dr Jones: Yes.

Dr Shreve:

Like CT will find six lesions – they must be calling non-specific lesions that aren't proven, I can't see any other reason.

Dr Conti:

What happens frequently is that you see these lesions and the report says suspicious for metastatic disease and that is the end of it. There is no further work up, because you are not going to go in and biopsy each one of these lesions.

Dr Shreve: It is completely meaningless.

Dr Sutcliffe:

I am actually going to actually hold us now on melanoma – I think we have got some very clear indications where there is total agreement and I think that some ongoing discussion that we need to have around depth of invasion in relation to staging. I think that we are pretty much in agreement on the other indications.

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Paediatrics

Speakers:

- ❖ *Dr Helen Nadel: BC Children’s Hospital*
 - ❖ *Dr Simon Sutcliffe: CEO, BC Cancer Agency*
 - ❖ *Dr Paul Shreve, MD: Assistant Professor, Internal Medicine, University of Michigan Medical Centre.*
-

Dr Nadel: (Part of main presentation)

So if we look at the practice guidelines, which would be recommended for paediatrics:

1. We have talked about brain tumours and that would be in basically assessment of recurrence verses radiation necrosis
2. Lymphoma is well established
3. In the sarcomas we would be looking at response to therapy, recurrence in the operative site, and metastatic spread.
4. Dr Shreve mentioned neuroblastoma, there is a group of patients who do present with MIBG negative lesions and this would be another indication.

Thank you.

Dr Sutcliffe:

I am just going to Paediatrics now I think perhaps if I may summarize and tell me if you disagree. It would seem that probably we are saying there really isn’t enough literature or experience to actually come across with strong evidence based guidelines for the use of PET in paediatric malignancies. Certainly it would appear that the brain tumours which are a common site – the issue of recurrence verses necrosis remains a very dominant reason for exploring PET and by analogy with other precedents in adult cancer, lymphoma would seem to be likely strong indication for the use of PET. Similarly sarcoma and neuroblastoma, seem to be sites where clinical sites are justified even though the evidence is not yet there to give chapter and verse on its utilization. Would that be a reasonable synopsis from our expert faculty for where that stands? Any questions or further observations on those sites?

Dr Shreve:

Well I think the point that I made that children are a special case and that you could make a special case for a special funding for a certain allocation of scans for a certain number of paediatric patients so that you can gain experience. To wait for definitive data, it could be five years, which I think is a disservice to that population.

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Unknown Primary Tumours

Speakers:

- ❖ *Dr Amanda Jones: Medical Oncology, Vancouver Cancer Centre*
- ❖ *Dr Simon Sutcliffe: CEO, BC Cancer Agency*
- ❖ *Dr Peter Conti, MD: Associate Professor of Radiology, Clinical Pharmacy and Biomedical Engineering USC*
- ❖ *Dr Paul Shreve, MD: Assistant Professor, Internal Medicine, University of Michigan Medical Centre.*
- ❖ *Dr Richard Wahl, MD: Director of Nuclear Medicine, John Hopkins University*
- ❖ *Dr, Dr Richard Baum PhD: Chairman PET Centre, Zentralklinik, Bad Berka, Germany*

Dr Sutcliffe:

Thanks, I would just like to just finish up now with Primary Unknown. We talked about cervical nodes and suspected Head and Neck cancer where we felt that that was a strong indication for PET. In Primary Unknown in general the recommendation is that PET scanning is an appropriate procedure. Any equivocation about that or any concerns or interpretations?

Dr Wahl:

Well I hate to be negative, but if you want to take an evidence base there are only about two papers about it. I think clearly we need to grow the literature and if you do allow it to be done here I think it would be useful to see how often it does change what is done for the patient. Some do take a more nihilistic view on this in that if you can't figure out where it is from then it may not make a whole lot of difference in most instances although. So I would say the evidence isn't as strong there as I feel it is in some of the other conditions though I would certainly not be opposed to it being applied carefully.

Dr Sutcliffe: Other comments? Joe?

Dr Connors:

Yes, I just want to pursue that a little bit because I think there is a big difference between identifying the primary and actually finding out something that is of clinical utility for the patient in cancer of Unknown Primary. It's the aspect of managing these patients that has bedevilled caring for them for the whole time that they have been defined as a separate entity and it is not infrequent that one does actually define the primary with absolutely no utility to the patient whatsoever. So I would want to narrow that down, or extract more from the data, and find out how often the patients actually have treatable primaries discovered that is treatable in the sense of disease that you can meaningfully manage or modify the natural history of metastatic disease once you discover it. And I suspect that that one third of patients that are found to have primaries would shrink to one tenth perhaps (?) of times when you actually find out they have an illness that you can change the natural history in a meaningful fashion. In which case you would be doing 10 PET scans for each time you found one that was of any utility in the patient at all.

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Dr Conti:

This is an interesting paradox in a sense because you have a situation potentially where you can do a PET scan to find a primary and you are saying basically that might not be able to do much with that PET as far as patient management but interestingly that the same time that you are doing PET scans to look for the primary you are also potentially staging the disease so you may in fact find the primary, find the diagnosis and also determine whether or not, given that new cancer that you have identified is in fact treatable or not treatable. So for example lets say it was a thyroid cancer for the sake of argument and you were able to resect disease. Then it would be potentially a curable cancer from that patients perspective on the other hand it might be something like metastatic carcinoma from another source and be completely incurable, in both cases you have identified the tumour and one might be treatable and not be treatable and even between those different types of cancers it is the extent of disease to determine whether or not you could manage the patient effectively. So it is a bit of a paradox in a sense. You could get the information to help you on both ends.

Dr Connors:

That is why I think it is necessary to characterize the question in terms of seeking additional information on those situations where you can conceive of it modifying further treatment.

Dr Sutcliffe: Dr Wahl? Dr Shreve? Dr Jones?

Dr Wahl:

Lets see. The kind of interesting issue though, it seems like the oncologists in the room all know the standard work up of the cancer of unknown primary. So probably unhesitatingly are going ahead and doing that CT and the whole body, mammogram, additional studies, may be not so but I would just say for those who aren't that is the logic that would seem reasonable because if you are going through the full work up it would seem that PET would also be a rational part of the full work up of an unknown primary. So it seems like the decision might be to come up even earlier in your thought process when you are using conventional diagnostic methods. If you are going to go through all those it seems only reasonable to do PET because there is an incremental yield but if you don't think that it is going to make any difference where this primary is from then you might question why do the CTs and everything else.

Floor:

Just a plea to be a bit more rational in the selection of PET scanning in the assessment of patients during follow up for example I don't take care of patients with GI malignancies but my suspicion is that if the CEA is rising rapidly 3 or 4 months after primary treatment, that that patient isn't likely to have salvageable disease unifocal metastases that are amenable to high grade palliation. In contrast in someone whose CEA starts to rise 18 months or 2 years after the completion of primary treatment and not to discount the value of follow up but to try and employ the circumstances where there is some biological potential to really make a difference with the treatment.

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Dr Jones:

I think I'd just like to reiterate that I. There is so little literature available on the Primary Unknown with metastases to sites other than cervical nodes that I think that this is a research area really rather than a primary tool. I think it does have a roll where you may be thinking of a surgical procedure on a patient with primary unknown, where you think that the primary say metastasis in the liver may actually be rather than a metastatic adenocarcinoma it may be a paracellular carcinoma and you may be looking at a surgical procedure, I think it has a roll already but I think with respect to the utility of making a diagnosis of a primary that is something that should be really part for a research protocol.

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Thyroid Cancer

Speakers:

- ❖ *Dr Helen Anderson, Medical Oncology, Vancouver Cancer Centre*
- ❖ *Dr Simon Sutcliffe: CEO, BC Cancer Agency*
- ❖ *Dr Peter Conti, MD: Associate Professor of Radiology, Clinical Pharmacy and Biomedical Engineering USC*
- ❖ *Dr Paul Shreve, MD: Assistant Professor, Internal Medicine, University of Michigan Medical Centre.*
- ❖ *Dr Richard Wahl, MD: Director of Nuclear Medicine, John Hopkins University*
- ❖ *Dr, Dr Richard Baum PhD: Chairman PET Centre, Zentralklinik, Bad Berka, Germany*

Dr Anderson: *(Part of main presentation)*

So to summarize Thyroid cancer:

- ❖ There is a high level of evidence that PET is useful where post treatment thyroglobulin is elevated and radioiodine scans are negative.
- ❖ There is some evidence in the literature that there may be a role for PET as an additional imaging procedure where the radioiodine scan is positive.
- ❖ PET may detect fully differentiated clones of cells that are missed by this scan. I would be interested in any of the panel’s comments about whether this is actually being used in their centres. And then the other indications for Thyroid cancer are still under investigation.

So to summarise in Head and Neck cancer:

- ❖ There is good evidence for its use in the detection of unknown primary.
- ❖ It is useful for the detection of recurrent disease but as we heard before it should not be performed too soon after radiotherapy, as false positives can be a problem with the inflammation associated with radiotherapy.
- ❖ Finally it may be useful in selected patients for staging where it can affect treatment planning and potentially affect outcomes.

Dr Sutcliffe: Thank you very much Helen.

Discussion Following:

Dr Sutcliffe:

I am going to go onto thyroid cancer: now where I believe there was one strong indication put forward and that was the detection of recurrent disease after definitive therapy on the basis of elevated thyroglobulin in the presence of a negative radioiodine scan. Correct me if I have said that wrong. That was the one indication that I picked up on. Is there any question as to the appropriateness of that recommendation?

Dr Wahl:

The American Thyroid Association has prepared a document, I don’t know if you have seen the draft. I saw the draft recently, which they are sending to HCFA strongly urging

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Dr Wahl (cont.):

their support of PET in the detection of recurrent thyroid cancer. The draft I saw also included the less frequent but equally perhaps more vexing problem of rising calcitonin levels in patients with the history of medullary carcinoma of the thyroid, but this body was strongly in the support of the use of PET in Thyroid cancer.

Dr Conti:

Yes, I haven't published in that area myself. I was very appalled by the fact that HCFA did not approve but specifically called out the lack of support for thyroid cancer. I think that this is a completely under served population that could specifically benefit from the technology when the alternatives are minimal.

Dr Baum:

We are treating about 100 patients a year with thyroid cancer with radio-iodine and I must say we have now done routine studies, although in what you mentioned that could be an indication in addition to radio-iodine, and I think the most useful indications is in patients with elevated HGG and radio iodine negative whole body scan. But also you see the so-called flip-flop phenomenon of differentiated and undifferentiated lesions in quite a number of patients with follicular cancer and metastases where you detect significantly more disease especially in the bone, which might deserve treatment - also patients with a positive radio-iodine scan. So I think the story is not closed. But clearly, the one indication with the radioiodine negative scan is a very good indication.

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Closing Remarks

Dr Simon Sutcliffe, CEO and President of BC Cancer Agency:

I'd like to bring the session to a close. I'd just like to recap that the specific purpose of this day was to come up with guidelines. I think I am really quite encouraged that there has been a really high degree of concordance between the interpretation of the local experience, based upon our experience, with that of the International Faculty and the literature, and recognizing that there are management variations that can preclude the total concordance of guidelines, recognizing that in the absence of any dedicated funding for PET from Government it is likely that the government will be fairly conservative in starting up. So our guidelines will probably be fairly conservative. I still think with those comments, we probably still have a substantial body of agreement on what should be considered as the appropriate indications for PET to be funded through the Health Care System, representing the state of the art practice in oncology

The next steps for us will be to refine this to clear guidelines, which I think we can do fairly readily, to translate those into numbers of studies based upon BC population demographics and to put that proposal before the Ministry, with our strong statement that in open discussion and in the context of international experience and world literature, these would be the recommendations that we would make, and we would ask for initial funding for those particular indications.

And it is very clear, we need to go down that route very quickly because all of the BC, well the vast majority of the BC, work that you have seen today, has been done on philanthropic funding and clearly now I think we have passed the point where philanthropy should be paying for PET for indications where the international field feels it now is a state of the art procedure. So we will move along as rapidly as possible in that direction.

I'd like to thank IPET as a co-sponsor. I would like to thank our guest faculty, Drs Coleman, Baum, Conti, Shreve and Wahl. I think you will all join me in recognizing the depth and breadth of experience that they have brought, and the significant support that they have given to our thinking around the indications of PET. So please accept my thanks gentlemen - I am most appreciative of your joining us here today.

I would like to thank our local faculty and those who also were on our steering committee for putting this conference together: our sponsors – our colleagues at Siemens, CTI, ADAC Laboratories and PETNet, as well as IPET and the BCCA. And finally, I would like to thank all of you for working your way through this meeting and for joining us so fully in the audience participation and the discussion of the presentation material today. Thank you very much indeed.

And that concludes the session.

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