2002 Annual Update and Review of Carcinoid Disease

Transcript of lecture by;

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Dr. Warner: Thank you very much. Good afternoon everybody. It's a pleasure to be here and see so many familiar faces. In fact, if it weren't for the seriousness of the topic this could be sort of like a reunion.

As you can see, we're going to really get an update, at least my view of what is important. Can you all hear me OK now? Good. You see listed the subject. This is going to be an update and just a little bit of a review, but predominantly an update on what I think is important and relatively new and of interest to this group. It is assumed that you all have at least smattering of knowledge of what carcinoid disease is. I will very briefly review Carcinoid Syndrome for anybody who wants a summarization of that again. But I'm really interested in what the current thoughts are among those doctors who specialize in treating this condition, what the trends are in treatment and in research, and what the practices are in both diagnosing and managing.

For years this was considered to be a very indolent, slow-growing type of tumor and all of them, all of these tumors were considered to be pretty much the same, and that perpetuated a sort of a conservative approach to their management. It is becoming increasingly apparent that a good percentage of the tumors are more aggressive and that they can't all be treated with such an expectant approach. And indeed, even the more conservative oncologists are now beginning to become a little bit more aggressive in recognizing this.

I've got an assortment of observations that are of interest before we go into more meaty subjects. The term 'NET', which you may not all be that familiar with, stands for neuroendocrine tumor. This is a family of tumors which have certain common embryological origins. Carcinoid belongs to that family and indeed is by far the most frequent occurring of that group. But the other NETs, neuroendocrine tumors, are known well. Some are very, very dramatic, causing other symptoms different from the Carcinoid Syndrome, but causing symptoms due to their own production of an excess of one hormone or substance or another.

Now, as you can see there, 2% of all gastrointestinal pancreatic malignant tumors are indeed carcinoids. Carcinoids and NETs can be functioning or non-functioning, meaning they may produce hormones that cause symptoms or they may not. In fact, of the other neuroendocrine tumors besides carcinoid, maybe only a third actually produce hormones. Of the carcinoids, even less produce enough to cause symptoms. But as you will see and as many of you know, they still produce enough extra substances to elevate the level of these substances in the blood and that can be useful for both diagnosis and following. Microscopically, when a biopsy is taken, all of these tumors, both carcinoid and the other neuroendocrine tumors, look the same under standard microscopic examination. So the pathologist cannot clearly say, "Ah, that's a carcinoid", just looking at the routine stain. Several different types of special stain have to be done to determine just what type of neuroendocrine tumor is being looked at, whether this is indeed carcinoid or a neuroendocrine tumor in general. And then sometimes even the blood chemical products have to be measured. These so-called markers will also help tell what kind of a tumor we are dealing with.

Carcinoid, as you heard and as you know, is often misdiagnosed. In particular in recent years we've noted that a fair percentage of patients are diagnosed as irritable bowel syndrome, IBS, because of vague abdominal symptoms and nothing obvious on usual examinations. And that may last for years. Others are carried as IBD, inflammatory bowel disease, such as Crohn's disease, and even

treated as Crohn's for a long time until finally the true diagnosis is apparent because of the need for surgery and then everybody is surprised with the finding. As you heard, they are becoming less and less rare. I'll give you some statistics in a moment. And also, they are sometimes more malignant than previously thought. Indeed, about 20% of carcinoids are much more aggressive than the very slow growers.

The original term 'carcinoid' was applied by a German pathologist who first described these tumors in 1907, and that term means midway between carcinoma, which is the usual cancer, and adenoma, which is a purely benign type of growth. So carcinoid, if you wish, is like calling somebody who looks like a human being but really is not, a humanoid. It's an in-between.

Now, the site of origin can vary considerably. It can be in what's called the foregut, which means this is referring to embryologic origin. And this is very important because the source of origin or the site of origin determines to a large degree the type of response the tumor will have to different treatment and also how it will grow. Certain ones are much more malignant and aggressive than others, certain once respond better to certain drugs. So it's important to try to find out where it originates from. Foregut means the lung, the stomach, the pancreas, and the thymus gland. Midgut means the intestine from the duodenum, from below the duodenum on down, to the furthest-most part of the colon, and then beyond that is called hindgut, and that includes the left side of the colon and rectum.

The next consideration is this term 'typical' and 'atypical'. This is a designation that was given to lung carcinoids and depends upon certain features microscopically, whether there are more cells multiplying or less cells. And that term has been applied with the same criteria to carcinoids and neuroendocrine tumors from all sites of origin. and it appears to bear out, that is, when they are typical they tend to be slower growing, when they are atypical they tend to be more rapidly growing. And then there are categories even beyond that, that are less frequently encountered but are more aggressive. Making this determination requires special microscopic examinations of the tissue and staining. It is important, though, because again it predicts the likelihood of growth, behavior of the tumor, and that contributes to making decisions regarding treatment and management. Are we more aggressive? Are we sooner to do a surgery? Or what other treatment?

Some of the stains that are used you may have heard of KI-67 or MIB-1. These are stains that determine whether or not, or what the number of cells are that are undergoing active division at the time, multiplication, at the time of the testing. Other stains for vascular endothelial growth factor, D44, and a number of others that sort of sound like alphabet soup. Anyway, these are all stains for markers on the cells that help to tell the behavior of the tumors, and that means it helps in predicting, and that aids is deciding about treatment.

Where can a carcinoid begin from? Well, you know that the small bowel, the small intestine, is the most common, almost 40%. Of those in the small bowel, about one fifth will actually end up spreading to some other locations. And of those that do so, only one half will end with the Carcinoid Syndrome. The syndrome is really very uncommon but it's the most flamboyant feature of the tumor so we hear about it the most. The appendix is next most common in frequency, a little over one quarter of the cases, and indeed, 1 out of every 200 or 300 removed appendices at surgery will be found usually coincidentally to have a carcinoid tumor. The size of the tumor is very important because the little ones are rather innocuous, the big ones are not and often require further surgery. The lung, the bronchial tree, some 10-15% arise there; the colon, not many, 3%; and then the stomach, a rather small number but very important because there are 3 types in the stomach and this is very important for the doctor to differentiate. Those that arise in association with pernicious anemia or so-called immune gastritis are very, very innocuous, only a smattering ever grow big enough to spread or cause trouble and these are associated with other glandular changes that can be treated one way or another. I won't go into that at the moment.

The next type in the stomach are the sporadic. These are tumors that occur willy nilly, without any obvious cause, as they do usually in the small intestine, and they are about 50% likely to spread. And then finally those associated with the multiple endocrine neoplasia syndrome, MEN syndrome. This is an inherited, genetically determined syndrome in which multiple tumors occur in different endocrine glands. And when these tumors are associated with gastric carcinoids they have a

malignant potential but the treatment is complicated because of the other associated tumors. The pancreas is only rarely a site for carcinoid, which may come as a surprise. Pancreatic carcinoid comprise only 2-5% of all the pancreatic neuroendocrine tumors. There is a mistake, often perpetuated by the pathologist, when he reads a pancreatic tumor biopsy as carcinoid because the tendency is to diagnose all tumors that look like that as carcinoid since they are the most common of all these neuroendocrine tumors. Special stains, as you've heard before, will help differentiate. Liver, gallbladder, bile ducts can rarely be sites of origin and then a bunch of other rare and unknown sites, are really very peculiar. The breast, the prostate gland, the kidneys, the uterus, the ovaries, even the wax glands, the cerumen glands in the ear, have been a site for the carcinoid tumor to originate in. These are really very uncommon and oddities.

Now as to the frequency. In the last few years it has become apparent that there are roughly 20 new clinically significant reported carcinoid tumor cases in United States per year per million in the general population. That computes out to maybe four to five thousand new cases per year. Since the survival is greater than, much greater, than the rate of attrition in these cases, the number of patients walking around is building up so we probably have between forty and sixty thousand carcinoids of clinical significance in this country at the present time. As I said before it's the most common by far of all the other gastro/entero pancreatic neuroendocrine tumors occurring, at least two or three times more frequent. And as we said, only a small number of those from the pancreas, though, actually are carcinoids.

Now, some other features of interest. It has been found out by statistical studies that another type of cancer, colon cancer for example, occurs with at 25% frequency at some time during the life of a patient having carcinoid. If it occurs earlier or after it is called metachronous. If it occurs at the same time then it's called synchronous. But 25%, one-fourth of all carcinoid patients, will come down with a colon, lung, breast or prostate cancer and that high frequency means that people with carcinoid should have a very much more assiduously performed annual examination looking to screen them for these other possibilities. Meaning, the men should have a PSA and the women mammography. A colonoscopy should be done at appropriate intervals also. So here we see the importance of the annual general exam. It should be much emphasized.

For those who want a little brush up on Carcinoid Syndrome, I've listed the major features, which most of you know. Flushing. The next is diarrhea. They need not both be present. You can have only one of the features, you don't have to have all of them. After you have this condition for a while you begin to develop venous telangiectasia, little spidery blood vessels on the cheeks or nose, because of the chronic stimulation of the serotonin on the blood vessels to open up. In a small number of patients asthma, bronchospasm will occur due to the effects on the bronchial tree of the products of the tumor.

Cardiac manifestations are particularly important, occurring in over 50% of patients when the disease is well advanced. There are 3 types of heart problems that come up. One is a sneaky, insidious type of heart failure due to the excessive stimulation of the heart by serotonin, bradykinin and other products of the tumor, without any anatomical changes. You don't see anything on the X-ray, you don't hear a murmur, etc. The second is actual metastases, the spread of tumor to the pericardium, the lining around the heart or the heart muscle itself. And that occurs in about 5% of patients.

The final one which is valvular disease, most characteristically affecting the valves on the right side of the heart, is pathagnomonic, that is, it is specific for carcinoid. That type of heart valve trouble causes swelling of the feet, fatigue, collection of fluid in the abdomen and can be cured in many instances by replacing the heart valve. And finally, most patients will have enlargement of the liver due to the spread of tumor in the liver where there is enough volume of the tumor to produce enough of the hormones to cause these troubles. Minor features; peptic ulcer in 1/4 of the cases, very low blood serum albumin, and even deficiency of the amino acid tryptophan, which causes a deficiency of niacin that leads to the condition called pellagra. Pellagra is characterized by diarrhea, dermatitis (a skin rash) and mental changes, dementia. And we certainly don't need that on top of Carcinoid Syndrome. This is why we recommend extra niacin to supplement the diet all carcinoid patients, that is, all those with the syndrome. Muscle wasting may be excessive, joint pains, a degeneration of the muscles, and intense scarring, fibrosis. In fact the fibrosis, which is stimulated by

the levels of serotonin which stimulate the fibroblasts , the cells which form fibrous tissue. Fibrosis can exceed in its symptoms the growth of the tumor so that we can have the bowel kinked or pinched because of scar tissues as the result of just a little tiny tumor in the intestine. Edema that persists in the feet may occur. And finally, hyperglycemia. That means that sugar, carbohydrate metabolism, will be impaired in many patients with Carcinoid Syndrome. If they have diabetes it will get worse. If they don't have diabetes it might dispose them towards this.

Now let's go on to some newer things. Actual genetic or inherited carcinoid or the MEN syndrome as a cause of carcinoid is very, very uncommon, only occurring in 4% or less of carcinoids. But nonetheless, it's exceedingly important to those who have it and to their offspring because they are at risk. And the question is, how do we tell? Well, it's obvious if there is a family history and you know your aunt and your father or your grandfather had a carcinoid, or other relatives. Then you're obviously under suspicion for this. And then your children are a concern. What can we do about that? Well, we'll come back to that in a moment.

Liver metastases can occur in about 10% of all patients, with or without the syndrome, without the primary site being apparent; not apparent by X-ray, standard X-rays or scans, etc. And as you heard before, it is useful to know where the tumor originated from in order to aid decision making in terms of treatment.

OK, both of these types of cases may benefit by a very, very new technique just released and approved by the FDA in the last 6 months. It's called 'wireless capsule endoscopy'. Just like we could do a gastroscopy or a colonoscopy with a fiber optic device with a camera at the end and see the interior of the intestine, now with this device which is a capsule that takes pictures and sends signals back to a recorder, that can be seen on a monitor, and that too is used. Here I have one. You see that little light that's flashing? Each time the light flashes it's taking a picture. And this capsule is no bigger than a large vitamin pill. And you swallow it. And you are hooked up to a harness like a cardiogram is being taken and a tape recorder like a Halter monitor, and it just simply takes pictures as it goes down, records it. And at the end of the day you take off the apparatus, give it to the doctor who hooks it up to his computer, and on his monitor he gets a moving picture of your entire intestinal tract. And can help to find the primary tumor. And if you know that your mother, your uncle, your grandfather had small bowel carcinoid and you have it too, this would be useful to help screen the offspring, to try to find it. Sometimes it takes years before the tumor manifests and then sometimes it's too late to tell. So, this is a very useful new development for early diagnosis..

And here, to show you, a section of the intestine that has been split open lengthwise, and you see the little tiny carcinoid tumors underneath the lining. This is almost impossible to see on standard X-ray, it's too small to pick up on a CT scan, and you might not even pick it up on an octreoscan. This new technique offers the promise to help diagnose when those little lesions are present and, I might add, we've used it for that purpose successfully in some cases.

Now here's a little more on that capsule. It's disposable. You don't have to retrieve it. It just gets flushed down the toilet at the end of the exam Here's a close-up picture of it. Here in cross section you see its size in comparison with a dime. It's half the size or less. You can swallow it if you can swallow a pill. Here again, the capsule, the recorder, the antenna and the monitor, and the harness that's worn during the day with this device. And here, not very easy to see, is one of the pictures that shows a tumor. This Y-shaped darker area is the cavity of the channel of the intestine and this bulging mound here is a tumor.

OK, now onto a different tack. The question is, why should we do these complicated and often expensive measurements of these different hormonal chemical substances in the blood, especially when you know the diagnosis. What use is it? Well, nowadays chromogranin-A is considered the gold standard and really has been accepted, properly so, to be used to monitor carcinoid tumors. Some of the reasons, aside from diagnosis by finding a high blood serotonin or a high urine 5-HIAA, the waste product of serotonin. Some of the other purposes are to help evaluate for MEN. Now we can measure other endocrine products from other neuroendocrine tumors such as gastrin, VIP, calcitonin, and a bunch of other substances, all of which are produced by the different neuroendocrine tumors. And if you find that one of these is elevated, along with the product of carcinoid, then an MEN Syndrome can be suspected.

Another very important reason for measuring, especially in patients who do not have Carcinoid Syndrome but have carcinoid, is that they will usually be producing at least a little bit more than normal serotonin or these other hormones and don't have symptoms. Under stressful conditions such as surgery, for the first time they may manifest a true carcinoid crisis, one of these episodes of intense flushing and wild changes in blood pressure and pulse rate and maybe bronchospasm too. Well, the time of surgery is not when you want that to happen for the first time and certainly your doctor and anesthetist want to know in advance. If you measure these substances before any surgery and find them elevated then you are forewarned and appropriate precautions can be taken. Such as, for example simply giving a dose of Sandostatin. Then again, we also want to establish parameters to follow if there is going to be an operation and a carcinoid is going to be taken out, we'd like to know that it's all out or how much of it is out. Well, if you measure these substances - chromogranin-A, serotonin, for example, neurone-specific enolase, Substance-P, these are some of the main ones - then you can see what the levels are before, you can compare following the surgery and over a period of time, 6 months or a year, you can repeat checking on them and see if something is coming back. These chemical substances very often will indicate the occurrence of a tumor before it's seen on any of the X-rays or imaging, so that it's an important way of knowing what is going on and knowing it quickly.

Regarding the natural course. I want to emphasize, these figures are what occurs when there is no treatment at all, not even Sandostatin. They come from the pre-Sandostatin era, before 1990. The average survival in a carcinoid patient, without the Syndrome, but once diagnosed, was about 7 years. But you have to remember, all these figures are not very tight in the range. The range is tremendously wide. So there will be patients who survive only a year or two, and there will be patients who survive 20 years. The average survival from the onset of symptoms from an untreated Carcinoid Syndrome patient, 3 years. From the time the diagnosis is made, without any treatment, 2 years. Again, I emphasize a wide range, but as you can see the average patients takes at least a year before the diagnosis is made and, as you know, very often longer.

Now, in the untreated patients, what are the causes of death? 50% will succumb to some sort of cardiac problem, for the reasons I told you before. 25% will succumb to the effects of the excessive hormones stimulating their digestive tract, to have excessive diarrhea or interfering with kidney function, or weakening their immunity so that they get infections, etc. And only 1/4 will actually succumb to the spread of the tumor, like an ordinary cancer. Now, these figures have changed in the last decade because of the advent of more treatments, or more effective treatments. What's happened is very, very much fewer patients succumb to cardiac effects or to the pharmacologic effects of the Syndrome, but now rather to the spread of the tumor. So, one of our main areas of interest now is to try to more effectively inhibit the growth of these tumors.

Some of the factors involved in survival prognosis are: the primary site, as I told you before, and listed in order of decreasing order of benignity: appendix most benign, pancreas more malignant. The size. If the tumor, regardless of where it arises, is less than 2cm it is better, if it's 1.5cm to 2cm or greater there is a bout a 75% chance of the development of metastases. This is at the time of original diagnosis.

The depth of invasion of the tissues in which the tumor arises. If it arises in the intestine and is only under the lining, that's not too bad. But if it's penetrated or grown through the muscle coat through the wall of the intestine, that is worse because it increases the chances of its spreading. And, of course, if it involves lymph nodes, that too means that there is a less favorable prognosis. It doesn't mean that it is impossible that a cure has been effective but it just shifts the odds a bit. Again, under the microscope, the growth pattern, the appearance is important because there are different types of growth patterns that the pathologist can report on and observe, and they relate to the aggressiveness or malignancy of the tumor, just as you look at the façade of a building and see the pattern of the bricks, he sees the pattern that the cells make in these tumors, and certain patterns mean a worse prognosis.

If a patient has the syndrome, the Carcinoid Syndrome, then the outlook is worse than without the Syndrome for the reasons I've explained. And again, I emphasize a wide variation in similar cases. This also makes it very difficult to do clinical studies comparing patients treated with one drug vs.

patients not treated, It's so hard to compare, there are almost no 2 cases that are alike.

Now, another new area. The standard imaging techniques that have been used, that you are all familiar with, are routine X-rays, a regular chest X-ray, GI series. CT scans, that's been very helpful. MRI scans, that's helpful. Ultrasound scans, that's sonography including EUS, endoscopic ultrasound where they take a scan from the tip of a gastroscope that's been passed down into your stomach and into the duodenum beyond, and can scan internally the pancreas which is right next to it. This is very useful in picking up very tiny lesions in the pancreas but the problem is that it can pick up lesions so small that they may be insignificant, so this also is going to take some getting used to, to know what is important and not to jump at every single shadow that is seen.

Routine isotope bone scan that uses an isotope called technicium, is helpful but not very specific. Octreoscan is very important, also known as SRS. This scan, which has now been in use for 6 to 7 years and is really the gold standard for imaging carcinoid and other neuroendocrine tumors, depends upon the presence on the surface of a tumor cell of a receptor, a particular type of receptor called the somatostatin receptor. And from that comes the term SRS, standing for Somatostatin Receptor Scintigraphy, meaning isotope scan of somatostatin receptors. This is fairly specific for neuroendocrine receptors since these receptors are present on 85-90% of all of these types of tumor cells. So a small percentage will be negative on the scan, another larger amount will be positive, and don't confuse the presence of Carcinoid Syndrome with a positive or negative octreoscan. These receptors have nothing to do with whether the patient has an endocrinologically active tumor. You don't have to be making serotonin to have a positive octreoscan.

Now, for a moment I'll digress to talk about other types of isotope imaging for neuroendocrine tumors. We mentioned OctreoScan. Neotect is another type of scan using a different isotope which is useful for tumors in the chest, that are negative on octreoscan but really suspected for being neuroendocrine tumors, and this, which is an approved scan, will be of help every now and then. An older type of scan involves MIBG to which an iodine isotope is attached. This will be positive in the majority of tumors called pheochromocytoma. They are tumors that make adrenaline-type substances and are part of the neuroendocrine tumor spectrum, and it will be positive in less than 50% of carcinoids. It is very popular in Europe, it is still investigative in this country though it has been around for 25 years. There is even a form of treatment with MIBG where larger doses of this radioactive isotope are given. More frequent is the use of PET scan, call FDG, which is not so helpful for carcinoid and I won't go into the reasons why, but there are some newer types of PET scan but the FDG PET scan is not helpful. There is also a technicium-99 VIP scan, that's vasoactive intestinal peptide, this is experimental but very useful. There is a F-18 DOPA PET scan which is another type, and a C11L5-HTP PET scan. These all are dependent upon rather complex chemical reactions in the tumors but can be helpful when the standard OctreoScan is negative and these are all presently in the works and will be available for use within a year or 2.

Now, to go on with the imaging. Here is the standard CT scan, and this CT scan shows you, an X-ray of a cross section through the torso, and this big structure here is the liver. These dark shadows in it, each one represents metastatic carcinoid in the liver tissue. Now, that's a standard CT scan.

And now we go to OctreoScan. Certain normal organs will take up the radioactive isotope that is injected and so they appear dark on the scan, and so will tumors appear dark, and sometimes it's difficult to distinguish. In this instance, this is a spleen, this is a kidney, this is a kidney, and this is a liver. There is a little smudge of a spot here in the chest, you can see the patient's head here faintly, and this clear area is the chest and there is a little spot, that's in the lung. This is in the urinary bladder because the isotope is excreted in the urine and this is waste material with isotope in the intestine. You can see the problems in interpreting this. It's not that precise.

Here is another instance, and this a little clearer. Here is background radiation in a kidney, again in the kidney, in the spleen, and here in the liver is a big dark spot of isotope, again one in the lung, a big one here in the root of the mesentery of the intestine. This is normal in the bladder but these are 2 masses in the pelvis and this is a tumor spread to the bone, to the femur, down here. Not all of these lesions were known of ahead of time, so this scan was useful in showing us where there were tumors and avoiding unnecessary surgery or a treatment that might not have been useful.

What are the uses for OctreoScan, somatostatin-receptor scintigraphy? Obviously, to detect and localize primary tumors, to stage them so you can know where it's spread or to help you decide treatment, to monitor progression or regression in response to treatment, to help select patients for liver transplant. We don't do liver transplants very often but in the instances where it would even be considered, if you found hidden tumor at a site outside the liver that would help speak against trying to cure that patient or help significantly by replacing the liver with a transplant. It is useful to predict response to somatostatin-type of drugs such as Sandostatin or octreotide. Because, if there are receptors on the tumor that pick up the isotope and you get a positive OctreoScan, then you can predict the better than 90% chance there will also be a favorable response to Sandostatin. And also, nowadays we are doing experimental treatment with radioactive isotopes and they're bound to a similar type of drug which is attracted to the tumors and hence give intense internal radiation. That won't be very effective if the tumors don't have a positive OctreoScan, so it helps to predict suitability for that type of treatment.

In a patient who has tumor demonstrated and known by other techniques, and has an absolutely negative OctreoScan, that would suggest you've got to treat them in some other fashion, which means you might have to turn to more aggressive surgery, or more aggressive chemotherapy, than the treatment that might utilize Sandostatin. We have a special hand-held gamma-detecting probe that detects radiation, it's like an oversize knitting needle, that they put inside the abdomen when it's opened up at the time of surgery, the patient having been given a dose of the radioactive isotope ahead of time, and find very small occult tumors that might not otherwise have been detected and take them out. So this is another advance.

There are some caveats in that the intensity of the OctreoScan finding is not related to the size of the tumor. You can have a little tumor with lots of receptors and a big tumor with only a few, so it's not the size, and I said it's not related to endocrine function. Not all the metastases, all the primary tumors will light up in a given case. Sometimes only a few of the tumors will. And then, certain things can make the receptors decrease. Certain chemotherapy of Prednisone treatment will make the receptors atrophy or shrivel up. Then, of course, if the patient is on treatment with octreotide/Sandostatin that will block all the receptors, you will get a false negative OctreoScan. All of these factors have to be borne in mind by your doctor when an OctreoScan is done.

Now, very quickly in the remaining time a few more words about treatment. I arbitrarily divide treatment into 3 categories, supportive, surgery and anti-proliferative. You notice I don't say chemotherapy, I say anti-proliferative, because there are other types of non-chemotherapy that prevent the growth or reverse the growth of tumors. Here listed are not all but most of the more important newer drugs and techniques. Endostatin, which is undergoing clinical trials now, is a drug that inhibits angiogenesis, new blood vessel formation. Tumors cannot grow unless they get a blood supply, and Endostatin appears to be useful for that purpose and initial trials suggest it is particularly useful for tumors that are highly vascular. Carcinoid is one of those. Thalidomide also has a anti-angiogenesis effect and it's undergoing trials but it's also available for general use, though it's unproven by formal clinical trial yet. Anecdotal observation has been favorable. Xeloda, which is an oral form of 5-FU, works in a similar fashion, on both angiogenesis and on cell division as a regular chemotherapy drug would, and often is given in combination with Thalidomide. In larger doses both of these drugs have very potent and unpleasant side effects. In small doses they are often tolerated. They are slow to work but in low dosage are looking very promising. There are some other agents which don't work in the same fashion and don't even have names yet, just research designations: PS-341. Irinotecan, which was known as CPT-11, is in use now and is particularly favored in treating colon cancer and it seems like it's promising in carcinoid too.

Another aspect of chemotherapy that we've learned is that modifying the dosage schedule, particularly when streptozotocin is used or other agents will have a very beneficial effect on the response to the treatment. You know, with most chemotherapy these tumor cells are susceptible to the chemotherapy only during a very specific phase of the cell cycle, the cell cycle meaning it's going through a process of dividing and replicating. Just like in nature, there is a cycle for vegetation for the tress to grow buds, then leaves, then shed, then new ones come on in the next season. Well similarly there is a cell cycle and these chemotherapies only work at a particular phase in the cell cycle. Now, if you have a tumor that is not rapidly replicating, only a very small number of its cells will be in a vulnerable stage to respond to chemotherapy at any given time. And if you give them a

big slug of very potent whatever it is, chemotherapy, it doesn't matter how much you give, there are only a few cells in that whole tumor that are going to be susceptible to that treatment. Although all your healthy cells are going to respond to the side effects of the heavy chemotherapy. This is part of the problem in treating with aggressive chemotherapy in these tumors. However, it looks as if smaller doses that are less bothersome in terms of side effects, better tolerated, given at frequent intervals, given for a long, long time, much longer than you could tolerate the standard dosage of these agents, it looks as if that type of schedule is much more effective. And so, beginning awareness of this is setting in and this type of modification looks promising.

Another area that has interested me in particular has been cancer cell culture drug testing wherein, testing for resistance to various drugs, wherein cells from a tumor can be put into a culture medium and then tested against a variety of chemotherapeutic agents and the rate at which they die off, or don't, is determined. And so a sensitivity to the drugs, much as we test an antibiotic's sensitivity to infections, can be determined. This is not a new concept, it has been around for 20 years and has not been too popular or well seized upon, but my observation in some patients has been very favorable where it showed us, or suggested, several combinations of drugs we wouldn't have dreamed of otherwise. And then when the patients were treated with them they responded wonderfully. The only problem with this is it is not always an approved treatment, that is, testing is very expensive and the insurances don't usually pay for it.

Another advance has been radiofrequency ablation applied to lung tumors. Now, RFA has been used widely in the past few years in liver metastases and has been rather favorable in its effect, but now its beginning to be applied to various types of NET's in the chest..

HACE, hepatic artery chemoembolus injection involves catheterizing and then injecting one or more arteries supplying blood to tumors in the liver. Here is an example, we have injected a dye, this is the artery in the liver, and these dark blossoms are tumor blushes. These are areas of increased blood vessels that represent tumors, and this is what many tumors in the liver would look like when we do that catheterization. Then we inject our medicines, emboli and chemotherapy, and here is a picture after. And you see, there are no tumor blushes. These tumors have been clogged up with emboli, loaded with chemotherapy and they sit there and, we hope, deteriorate. And this is just the result of that kind of treatment. Basically, the majority of people will have a favorable response. The only problem is its done differently every place in the country that does it. And so, there is no uniform way of doing it. We think our results are very good here. We've had up to a four times greater survival longer than without doing such treatment. Because of the time, I'll stop at this point. We will have a question and answer period, and Susan Weiveris will tell you about that.

Susan Weiveris: Well, we had hoped to have a wireless mike to be able to come up to you in the audience but unfortunately that is not working but we have this microphone on the table that has a bit of a cord on it. So if you can just come down one at a time, raise your hand and we'll acknowledge you, you can come down and speak into the mike. Phil will help you with the microphone and Dr. Warner will address any questions you have.

Phil Bauman: OK, does anyone have any questions you'd like to address to the doctor?

Female Audience Member: I know that chromogranin is considered the best indicator of tumor load. Or I should say is chromogranin? It is my understanding is that chromogranin-A is the best indicator of tumor load. And if that's true, like what's the range? I mean, I have seen places where people have had chromogranin-A of 900 and something, or 40 something.

Warner: I understand. The question is that she understands that chromogranin-A is the best indicator of tumor volume, and yet she has seen a wide range of reports for the numbers on tests for chromogranin-A. First of all, it's positive, that is it's abnormal in 90% of the cases. There will be 10% where in spite of everything it's normal. We're not sure why that is but that's the way it is. The level will vary from patient to patient. There is no particular significance when you compare one patient with another. You may have one patient with a huge tumor (in fact I had one fellow who had a tumor of the liver that weighed 14 lbs. when it came out, and his chromogranin-A was only about 3 times the normal level.)You may have someone else who has a small tumor, maybe the size of an acorn, yet their chromogranin-A is 100 times greater than normal. So you can't compare one to another.

But, once getting the baseline in a given case then you use that for comparison as time goes by in that particular patient, and how it changes from their baseline level to how it changes later, that seems to be the most useful. This is also one of the reasons why, though CgA is the most dependable, we still like to measure the other markers. Sometimes there'll be something else that is even more useful; maybe it's the blood serotonin level which can fluctuate rather considerably in a given patient. It may be neuron-specific enolase or Substance-P. At some time in the course I think it's useful to do the whole panorama of markers, to try to find what are going to be the most dependable useful ones to follow.

Phil Bauman: Anyone else have some questions?

Female Audience Member: If the patient has extensive carcinoid in the liver would you still, would you recommend the hepatic embolization? And the other part of my question is, I've heard that it is extremely high-risk. Is that true?

Warner: The question was, if the patient has carcinoid in the liver would we recommend hepatic artery chemoembo. And the second question was is it true, as she's heard, that it's an extremely high-risk procedure. I'll answer the second question first. It is not an extremely high-risk procedure, assuming that the accepted criteria for doing it are followed. Nobody who has overt liver failure should be submitted to it. That's an obvious thing. And nobody who has a roaring fever or is very sick with other complications should be submitted, etc. But assuming the criteria that would allow the patient to be acceptable are followed, and then it is not high-risk. As I said, it is done differently in almost every institution in the country, using different drugs or different doses of the same drug. There is really no uniformity of how it is done, which helps to explain why there is not such a good uniformity in the results either. But among those who do a lot of it, and there are perhaps a dozen or so such institutions and we are one of them, among this group, even though we still vary a little bit in how we do it, our results are excellent. We, from Mount Sinai reported at a national meeting of invasive radiologists, last March, on the outcome of 176 hepatic artery chemoembo treatments. We had 1 death, which was expected, in a patient about a week later because this was a person who had waited and waited and waited for 2 years, in spite of continuous recommendations for the treatment. An then when the patient was very desperately ill the family pleaded "please do it, do it now". And we said it's not going to be very successful and we're afraid, and they said "what's to be lost, then do it", and he succumbed due to liver failure a week later. But we've had no other serious mishaps out of 176 procedures. So when done with appropriate caution it is a safe way, it is a safe form of treatment. I won't say it is without some pain and discomfort, but not unbearable, quite tolerable.

Female Audience Member: I just want to add to that. You said the results are four times better than without the treatment. What does that mean basically?

Warner: I understand your question. I had said that the average survival following chemoembolus treatment, if followed up with some type of systemic treatment which usually included Sandostatin, resulted in a survival of about four times longer in the group of patients thus treated than it did in as close to a similar group that we could get that had no treatment. That's what I mean.

Female Audience Member: So what do you mean by length of time?

Warner: I mean how long they lived from the time the treatment was done until they died.

Female Audience Member: Was this like months or years?

Warner: No. This is in years. In fact many of the patients treated by HACE survive a long time. We have been doing this type of treatment since the 1960's and I believe we've still got a couple a patients that we did then that are still alive.

Unidentified Male: There was someone on a list the other day that said that they took a survey that said there were 3 people diagnosed with carcinoid that had lived since 1967, and I think he was the oldest one and there were 2 others that had over 25-30 of survival having known that they had carcinoid.

Warner: Yes. Of course a great deal depends upon the particular tumor. Some tumors would be very slow growing anyway so it is very difficult to know in a given case to know what the outcome would have been had they not had that treatment. And I doubt that there will be any careful controlled study of this type in the future because 1) there aren't that many patients around wishing to submit themselves to no treatment so they can be evaluated as comparisons.(control subjects) (Audience Laughter)

Female Audience Member: Are there data indicating that the use of Sandostatin, aside from relieving symptoms, will reduce the sclerosis in the heart.

Warner: The question was, are there data that indicate that the prolonged use of Sandostatin will help to reduce or prevent the development of the heart lesions. I am very happy to answer that question because it allows me to dilate a little bit upon Sandostatin, which I didn't get time to do. First of all, the occurrence of the valvular lesions in the heart has been, in a very well done study by Dr. Larry Kvols whose name may be known to many of you, shown to correlate with the endocrine activity of the tumor. Everybody who gets valvular heart disease has very high output of serotonin and a high urine 5-HIAA. And when you give prolonged treatment with Sandostatin the majority of patients thus treated will have inhibition of the production of these substances, and it looks as if it will thereby be able to prevent the development of the heart disease. This is one good reason, for example, why in an asymptomatic patient who has high levels of blood serotonin, it is still prudent to give this treatment because you are preventing this type of lesion from developing. Now another point that I would like to make is, lately it has been shown that Sandostatin is good, not only to control the symptoms of Carcinoid Syndrome by inhibiting these hormones but it has totally additional effects, anti-tumor effects. It inhibits other substances that seem to stimulate the tumor cell growth so giving Sandostatin, even in an OctreoScan-negative patient, probably helps to inhibited tumor growth, to what we call "stabilize it". Indeed the evidence of this occurring is so strong that the Novartis company has a trial going on now with a new Sandostatin preparation called Oncolar. Now many of you know the Sandostatin LAR, which is the long-acting roughly monthly injected form, as verses the standard which is given a couple of times a day and is only brief in its action. Well, the Oncolar is a preparation they are studying to be given once a month which contains 160mg, as verses the 30 which is the average standard dose of the regular Sandostatin LAR. So this mega dose has been shown in animal studies and it looks like it may do the same thing in man, to have a strong anti-tumor effect, which is one of the reasons why I favor people being treated with larger, rather than smaller doses. You know, in medicine in general, the idea is to treat with as little medicine, or as low a dose as you can get away with that is effective or relieves symptoms. In this instance the idea is to treat with as large a dose as you can manage because of its anti-tumor effects.

Warner: The same person, another question.

Female Audience Member: Considering the treatment of depression, we are often using the serotonin re-uptake inhibitors nowadays. And in some instances we're using Ritalin. Are there contraindications or can you continue to use these drugs?

Warner: Alright. This is an important point. For those who didn't hear it, the question was, concerning the use of drugs for depression in carcinoid, mood or psychotropic drugs. Some of the most important drugs for that purpose are harmful for Carcinoid Syndrome. The so-called serotonin re-uptake inhibitors such as Zoloft, for example. They will cause a provocation, can worsen Carcinoid Syndrome symptoms, so we don't like to use those drugs. There are other anti-depression drugs that are safe to use, that don't work in quite the same way. Remeron is one for example and is useful. And of the older drugs, the tricyclics such as Elavil were useful too. I'm sure that there will be new drugs developed that will also be of some benefit here. Ritalin, which can help as a stimulant, has no contraindication.

Warner: There was a question over there.

Male Audience Member: The drug injections that you say are definitely looking effective for tumor stabilization can be done for how long?

Warner: You're saying Sandostatin?

Male Audience Member: Yeah.

Warner: Alright. The question was, can Sandostatin be taken indefinitely? That's an interesting question because some physicians have proposed that it wears itself out after a year or two, which even antibodies form. But there are many patients who have taken it for a decade or more, and I know of patients who was on it while it was still experimental, and have taken it for like 15 or18 years. Occasionally, there are several reasons why it might begin to wear out its effectiveness. Not necessarily allergy or the development of antibodies, but rather, when it is taken for a long time there is some evidence that receptors on the cell surface, to which it binds and on which depend its action, may be downgraded, down-regulated, so the receptors become like a muscle that isn't exercised, they wither. When that happens, we have found that a holiday from the drug for a brief period allows recovery of responsiveness, and then it can be given again. Now, there is another aspect to it too. It goes the other way. We've found that some tumors that that don't have enough receptors to take up octreotide and to show on an OctreoScan, will after several months of treatment with Sandostatin then have their receptors up-regulated, in other words increased, so now they do take up and they show a positive OctreoScan. So which one is at play is a little puzzling. We do know there are other factors like, for instance, treatment with Prednisone down, depresses receptors. After chemotherapy receptors will be depressed. And this is important because if you use the OctreoScan to asses the effectiveness of chemotherapy and now you get a negative OctreoScan you could falsely think you had a great response to the chemotherapy and it might be that it just depressed the receptors. Another reason why you don't depend on one modality alone to assess what's going on. Thus we use CAT scans, markers, and so on. Each one, like the piece of a puzzle, put the pieces together and see the whole picture.

Susan Weiveris: Unfortunately, we only have time for one more question so, I know Phil has one but maybe you can get yours laterŠ

Warner: We have a question here.

Female Audience Member: Why do markers continue to go up with the treatment of Sandostatin?

Warner: Why do the markers go up with Sandostatin?

Female Audience Member: Continue to rise even though the person is on Sandostatin.

Warner: That's, that usually is an indication that it's ineffectual, that it's not exerting its influence effectively on regressing at least hormonal function in the tumor. I would expect if that's what's happening you must have had a negative OctreoScan, that this may be an instance where there is just a lack of receptors so the drug is just not working. It usually means ineffectual response to the drug.

Female Audience Member: Well, can it be because the dose is not high enough?

Warner: Occasionally yes, it can mean the dose is too small to work and you need to give a bigger dose, but even with a modest dose I would expect some sort of response. Thank you. Maybe we can meet outside during refreshment and I'll talk to you personally.

Female Audience Member: Thank you.

Susan Weiveris: I'm sure you'll all agree with me that that was a very informative and enlightening discussion by Dr. Warner. We probably could have him here for the whole day. But, thank you again very much doctor. We appreciate that.