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TRANSCRIPT FOR VIDEO #4: DIAGNOSIS AND TREATMENT OF GYN CARCINOSARCOMA—WITH DR. WHITFIELD GROWDEN
Interview, Massachusetts General Hospital
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Produced by The GCS Project

(WG—Whitfield Growden, MD; DR—Diane Redington, CRNP)

Slide: WHAT TRIALS TELL US ABOUT TREATMENT
Patient/Advocate, Diane Redington, and Dr. Whitfield Growden discuss the management of ovarian and uterine carcinosarcoma

DR: If you are diagnosed with carcinosarcoma and you're not a surgical candidate, how would you be able to differentiate between an ovarian and a uterine carcinosarcoma?

WG: That's a great question.
A lot of times we would want to do advanced imaging studies.

DR: Imaging. Based on a pattern of metastasis?

WG: No, probably not based on a pattern of metastasis, although that might help. A lot of times you would want to image the pelvis very carefully. Our practice here, whenever I take care of a new person that has carcinosarcoma suspected either of the uterus or the ovary, I consider getting a PET CT, generally up front. Generally with uterine carcinosarcoma, we know that the chances of having metastasis early is higher. And so, I do the PET CT to understand what's going on in the neck, the chest, the abdomen and the pelvis. And what the PET CT will do for me is, it will administer a sugar molecule that's attached to a phosphol that would glow brightly in the PET scanner. And cancer cells are much more likely to take up sugar, so that, in theory, things that glow bright would look positive possibly for cancer. It helps me actually map out what type of surgery I'm going to do. And a lot of times you can see abnormalities on the ovaries. You can see abnormalities within the uterus. For deep pelvic imaging, I will generally get an MRI. And sometimes I do both because I want to understand where's this growth appear to be coming from.

We still see metastasis to the uterus and even synchronous primaries [two different types of cancer occurring at the same time]. We see abnormalities on the ovary simultaneously with the uterus.

DR: That's synchronous metastasis versus…

WG: Right, and again, you can't tell—did this start in the ovary and go to the uterus or did this start in the uterus and go to the ovary? *Which is why we sort of use broad terms like Gynecologic Carcinosarcomas*. I think an important differentiation that you are getting at is, treatments might change based on whether or not you have an ovarian carcinosarcoma or a uterine carcinosarcoma.

DR: Could you talk about that? So, if you are diagnosed with an ovarian carcinosarcoma, could you take us through the stages of what you would do? When is it appropriate to have surgery versus when is it not useful? You could just talk about all the different treatment modalities.

WG: ***If we suspect that this is an ovarian carcinosarcoma, our treatment paradigm essentially mirrors that of epithelial ovarian cancer.*** What we generally do, is we do a good exam, we get good lab value testing—things like CA125, Carcino Embryonic Antigen, which is the CEA, and we sometimes get a CA 19-9. And we do that for all of our patients with any type of epithelial or suspected epithelial ovarian cancer.

And then what we'll do is we'll get imaging, because what we want to know is, are we able to do an upfront surgery or an interval surgery that will allow us to remove all the cancer cells? Sometimes ovarian carcinosarcomas affect tissues that we can't remove, and it wouldn't be safe to remove. And so I wouldn't recommend upfront surgery in that setting. I would want to give chemotherapy first.

The standard treatment for an ovarian carcinosarcoma would be giving conventional carboplatin and paclitaxel [Taxol] therapy.

With regards to intraperitoneal chemotherapy, this is a purely ovarian cancer modality that we use. And it's invariably used when we do an upfront surgery, remove the vast majority of cancer cells that we can see with our eyes, and then we put a port in either on the right or the left, and then we administer chemotherapy both in an IV as well as intraperitoneal in order to apply chemotherapy directly to the surfaces that are most likely to have residual microscopic cells. In several trials, this was associated with both progression-free and

overall survival benefits—by giving intraperitoneal as opposed to purely IV. *This is controversial, because all of those trials excluded women with carcinosarcoma.*

DR: Of course.

WG: But our practice here is that we look at that and say, *on a genomic level, ovarian carcinosarcomas appear to look like epithelial ovarian cancers,* so we offer women intraperitoneal chemotherapy here. And I have personally taken care of women who have done very well with intraperitoneal chemotherapy, and they've had as excellent outcomes as what we've seen with non-carcinosarcoma epithelial ovarian cancers. Again, because we think it's probably a variant of epithelial serous ovarian cancer, which is why we see good responses.

DR: Interesting, so… but it would only be following a surgical procedure, correct?

WG: With intraperitoneal, that's correct.

DR: So, and surgery's indicated for Stage 1, Stage 2. At what point do you decide?

WG: That's interesting. A lot of times, Stage 1, Stage 2, and Stage 3, we will offer a surgical procedure upfront with ovarian cancer, assuming their imaging looks like we can remove all the cancer cells. With Stage 4 disease, when we see evidence of either metastasis within the liver in places where you can't remove or…

DR: Within as opposed to a coating on the liver?

WG: Right, as opposed to a coating. Correct. Or we see chest disease, meaning basically lung metastasis, or brain metastasis or something that wouldn't be addressed with a surgical procedure in the abdomen, many doctors will go ahead and give chemotherapy up front, see a response in the chest or wherever else it is extra-abdominally and then pursue a surgical procedure in the abdomen. Once we feel like these cancer cells here have responded and are shrinking, and we have good therapy for that, then we would want to actually "cyto-reduce," is what we say—basically lower the burden of cancer cells in any given person so that the chemotherapy can be more effective.

DR: What about a para-aortic lymph node metastasis? Would that eliminate surgery or would that …?

WG: No, it would not. And that would be true of both uterine cancer, meaning uterine carcinosarcoma, as well as ovarian carcinosarcoma. A normal paradigm for me when I take care of women that have uterine carcinosarcoma is I'll get that PET CT, which will tell me about para-aortic lymph nodes, the pelvic lymph nodes, and then what I'll do is, I'll do a comprehensive laparoscopic staging procedure, which is where we remove the uterus, the ovaries, the fallopian tubes, the pelvic and the para-aortic lymph nodes and test them. We know that the rate of lymph node metastasis for carcinosarcoma is higher, sometimes upwards of 40% of the time with these high-grade carcinomas. And this helps us direct our future therapy. *Because even with Stage 1 carcinosarcomas, I recommend treatment with chemotherapy with uterine cancer, which is not true of other types of uterine cancers. We treat uterine carcinosarcomas differently. We tend to give them more chemotherapy up front. In the setting of lymph node metastasis, we also apply radiation therapy.* And this is targeted radiation therapy.

Now, I think that's another major difference in paradigm between ovarian carcinosarcoma and uterine carcinosarcoma. With uterine cancer, we have a much greater experience using radiation therapy. And we know that that can be a very important adjuvant that can reduce recurrence risk.

DR: So surgery, possibly intraperitoneal chemo ...

WG: For ovarian, correct.

DR: For ovarian. And then chemo, ongoing chemo or ...

WG: And then, we would do usually 6 cycles. We, in the …

DR: Only 6?

WG: In the upfront setting, we generally will give 6-7 cycles of chemotherapy for ovarian carcinosarcoma or uterine carcinosarcoma. And then we'll follow that up with some sort of an assessment, like an imaging study, to understand, "Is anything left over. Is there anything residual that we're concerned about?" And, if we don't see anything, we like to stop therapy. And the reason for that is that we don't want to tirelessly do more and more chemo. There are some older trials that suggested doing more chemo if there's no target just exhausts people and decreases a woman's functional status. So that such that if this were to come back, they might not be able to tolerate as much chemo. So lots

of times, we think about stopping. If we see something, then we talk about additional therapies. Then we talk about changing things and seeing whether or not we should be giving additional therapies.

DR: But the thing is, it always comes back. It always returns. So that window that you have where you've stopped chemotherapy now gives those microscopic cells an opportunity to grow. It's rare for it not to come back. So, I think, well why not just have some ongoing maintenance?

WG: I think that's a terrific idea.

DR: You're saying…but it sounds like what you are saying is it depletes the system so you ...

WG: So, a lot of maintenance strategies have been looked at. You're absolutely right. The real Holy Grail of oncology would be to give a medicine that gets rid of everything and then give a less toxic medicine that people can live on. Like Tamoxifen for breast cancer. That was a blockbuster, because it helped women. They were able to take something that meaningfully reduced their recurrence risk. We haven't found that for any type of ovarian cancer. We haven't found that for any type of uterine cancer. And so carcinosarcoma, which are more uncommon versions of both of those things, are probably even further off for having something like that. And right now, the therapies that we do have, women can't be sustained on. Even something like single agent Taxol was looked at in ovarian cancer. And what they found was that if you gave women a years worth of single agent Taxol after finishing upfront therapy, you did delay any recurrence, but you never stopped it. And when women developed that recurrence, it was unclear if they had enough reserve to do more necessary chemotherapy. And so you are bringing up the most important dilemma that we have.

DR: Well, the treatment failure and the recurrence rate is so high with these cancers, why not just start off with all guns blazing? I mean with a combination of chemotherapy, immunotherapy—give it all you got. So, what do you got to lose? Most of these women are going to die.

WG: Well, you bring up a very good point. And right now, the paradigm for ovarian cancer, meaning that we sort of have this clinical divide between the ovarian carcinosarcoma and the uterine carcinosarcoma. And 50% of women with uterine carcinosarcoma have Stage 1 disease, meaning it's confined to the uterus.

DR: Fifty percent?

WG: Fifty percent.

DR: Because it's easier to diagnose…?

WG: Well, yes, there's bleeding early. But even though 50% have Stage 1, in regular endometrial cancer, 85% are Stage 1.

DR: I see.

WG: Does that make sense?

DR: Yes.

WG: So the majority of endometrial cancer as a cohort—the 64,000 women diagnosed with that—majority of them, 85%, are Stage 1. But carcinosarcoma—it changes. But even those Stage 1s, as you've said, have a much higher recurrence risk. So, with Stage 1 endometrial carcinosarcoma, we give chemotherapy, and we don't do that for other types of endometrial cancers. And so we do get more aggressive. We also are more likely to give adjuvant radiation therapy. So, those are the two modalities that have been most tested. And so, we do tend to "throw the kitchen sink" at carcinosarcomas.

Unfortunately, there are clinical trails that have looked at this and have sort of lumped carcinosarcoma in with a group of higher-grade endometrial cancers. What they've found is that they haven't been able to meaningfully change the recurrence rate. Meaning the "kitchen sink" we have isn't getting the job done. It's tiring women out. Women feel like they are getting hit by the kitchen sink, but it doesn't appear to be moving the bar where we need it.