



Hosts

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Fertility and Cancer Treatments

Guest Expert:

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Yale Cancer Center Answers

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Welcome to Yale Cancer Center Answers with doctors Francine Foss and Lynn Wilson. Dr. Foss is a Professor of Medical Oncology and Dermatology, specializing in the treatment of lymphomas. Dr. Wilson is a Professor of Therapeutic Radiology and an expert in the use of radiation to treat lung cancers and cutaneous lymphomas. If you would like to join the conversation, you can contact the doctors directly. The address is canceranswers@yale.edu and the phone number is 1888-234-4YCC. This week, Lynn welcomes Dr. Pasquale Patrizio. Dr. Patrizio is Professor of Obstetrics, Gynecology, and Reproductive Sciences at Yale School of Medicine and Director of the Yale Fertility Center. Here is Lynn Wilson.

Wilson Let's start off by having you tell our audience a little bit about what you do with respect to patients with cancer?

Patrizio This is a very important topic of the discussion tonight. There are urgent needs for patients that are of reproductive age that have either not completed their family or not even started their family, that unfortunately, are diagnosed with cancer. Up until 12 years ago, there were not many options for these patients. Today, the field has completely been revolutionized by the possibility of offering many options for fertility preservations, and therefore, these patients that have been diagnosed with cancer, ideally before they start their cancer treatment, are referred to reproductive specialists and we discuss with them the opportunity to cryopreserve their future options for having a family after they survive the cancer.

Wilson How did you initially become interested in this field?

Patrizio Approximately 12 years ago or so, in talking with colleagues at scientific meetings, there was the observation that there was this urgent need to fill a void in our discipline. In other words, we are starting to see more and more young patients, women and men, surviving cancer and then coming to our practice asking for the opportunity to conceive after they were cleared from their oncologist, and 12 years ago, the field was not prepared to handle this type of patient, and then slowly but surely, with the effort of many of my other colleagues, we started to get together, and we created the fertility preservation society in the realm of the American Society for Reproductive Medicine, which was spearheaded by some other colleagues and myself. We were involved since the beginning, so it was really a need to fill a gap in our field of reproductive medicine together with the observations that more and more patients have been successfully able to beat cancer.

Wilson Obviously this is an enormous issue for many women who are undergoing cancer treatment or had cancer treatment, how are they generally put in contact with you? This is obviously really important, but a lot of patients may not even be aware of such expertise or such specialists?

Patrizio You are absolutely right. The work that has been done in the last decades has been monumental in

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this respect because the oncologists, the pediatric specialists, the reproductive medicine doctors, urologists, and so forth, they never had the opportunity to work together on a big issue such as this one which is a fertility preservation. So, by putting together a group of experts, in 2006 we wrote, together with the American Society of Clinical Oncology, the initial guidelines recommending and suggesting to oncologists that before they embark on proposing a chemotherapy protocol or radiotherapy protocol, to please be aware that there are options that women need to be informed about before they undergo cancer treatment, so that has been a great help. A second big help, if not even more important than the first one, has been coming from patient organizations and the one that started the process was created by Lindsay Beck, and she created an organization called Fertile Hope in New York and she started to disseminate among patients and among oncologists and reproductive specialists, the information that we need to take care of fertility issues at the outset, and this was joined by the Lance Armstrong Foundation and now there are so many more organizations that are patient driven, and they are really sensibilizing the public opinion on this very important issue. And thirdly, as specialists in the field, we are also networking with many other colleagues around the world in a way that the same information and the same options are going to be made available not only in the United States, but also in Europe and in other countries.

Wilson Have you found that other types of medical specialists, other physicians, have been responsive to these, what sound like, enormous efforts on your part and others to create awareness that your type of expertise is available? Have you seen an increase in referrals and in patients coming to you for help ever since these programs were initiated?

Patrizio Yes, here at the Yale Fertility Center we have seen an increase in referrals, and I can say that we have a very strong network and collaboration here with Yale Cancer Center, with the breast center along with the pediatric oncologists, and we are very much united in this. However, in some other centers it is a little bit more difficult because it is really a lot of work, like you said, it is a work that in order to be implemented you really need to have a structure behind, where the healthcare provider is invested in a completely different aspect of the treatment plan. So, ideally to facilitate the filling of this gap, it will be best to have someone that is responsible for talking, for discussing the options for fertility preservation. Let's say in an oncology practice, someone that is going to be designated as the person or a team of a couple of people that are going to take charge and help patients and start to inform them of the various options, the various centers that can provide these options, where are they located and so forth. But, as you said, it is really teamwork, it takes a lot of energy and a lot of resources and that is one of the problems that maybe we will discuss later, but that resources are not easily obtained for this type of work that is considered still experimental.

Wilson I think another issue may be that both for the patient and the oncology physician, when a new

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diagnosis of cancer is rendered, obviously that physician is very focused on their kind of treatment and their treatment plan for the patient and the patient is of course having a tremendous amount of anxiety and is focused on getting their cancer treated as effectively and quickly as possible and may not be thinking so much about fertility at that time, so I think it is even that much more important to make sure that doctors and teams of medical professionals appreciate the kind of service and consultative work that you provide. What would you say is an ideal candidate for fertility preservation, what would be an ideal scenario?

Patrizio An ideal scenario would be a young patient, post puberty, whether married and already had one child and still wants to preserve options for future children, or someone that hasn't had a chance to have a baby yet. They can be referred and listen to the vast array of options that we can offer to them, so ideally, before chemotherapy or radiotherapy is initiated, that will be the best time for having a consultation. Although, if this cannot be obtained because perhaps the initial diagnosis is rendering the patient so sick that there is no other possibility than starting the chemotherapy, then, as you know, chemotherapy goes in cycles and perhaps if there is a little hiatus, a little time, between cycles, we can intervene at that time as soon as the patient is stable and have the chance to be treated. Another problem that is also worthy to mention is that not every single type of cancer and every single type of chemotherapy is necessarily associated with infertility, or with the sterility of the cancer. However, it cannot be taken lightly thinking, okay I will have a full recovery after chemotherapy, because even though we may be confident that some cancer, particularly when they are diagnosed in the young age, are associated with a good chance of recovery of their menstrual function, it is important to have a discussion anyway because even though you recuperate and may recover the ovarian function, you may still suffer premature menopause, and therefore, this discussion is better to be entertained regardless of the mild type of chemotherapy that a patient is receiving.

Wilson It is a little bit of a tangential subject, but you mentioned premature menopause, for our audience, can you describe that?

Patrizio Premature menopause is when the ovarian function ceases before the age for it, so when a woman has no more menses and she is 40 or 41, while in North American Caucasian woman the age of menopause is about 51 or 52, when the function ceases 10 years before that, it is a premature menopause.

Wilson I see, and in terms of preserving fertility, assuming a woman is post puberty age, is age a significant factor, or is the likelihood of preserving fertility higher the younger the patient is?

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Patrizio Let me also elaborate a little bit more, the younger the age at the diagnosis, there are two pieces of good news. One is that perhaps the reproductive function may be more protected because there are many more eggs in the ovaries. And number two, even though the insult from chemotherapy is powerful enough that for a year or two years after the end of the chemotherapy the patient may be not having menses, there is a likelihood that those menses may return. So, the younger the age, the better the prognosis. If the woman is 35 or older, the chances that she may recuperate the ovarian function and the chance that she may still be able to have children with menstrual function that has been recuperated, is only 50% of what it would be if she had not have been diagnosed with cancer.

Wilson In your practice, what percentage of patients that you see are self referred, meaning the patient finds out about your expertise and makes an appointment for themselves as opposed to a physician referring that patient to your service?

Patrizio Prior to 2006, I would say it was 50-50, meaning 50% of patients were finding us via a patient advocacy organization, but after 2006, we now have about 80% of colleagues referring patients and only 20% are coming via internet or other organizations.

Wilson So a lot of that effort, which I know is ongoing, is to increase awareness and demonstrate that there are really experts, specifically in this field?

Patrizio Correct, there is still some more work to do, of course.

Wilson We are going to take a short break for medical minute. Please stay tuned to learn more information about fertility and cancer with Dr. Pasquale Patrizio.

*Medical
Minute*

The American Cancer Society estimates that over 1000 patients will be diagnosed with melanoma in Connecticut each year. While melanoma accounts for only about 4% of skin cancer cases, it causes the most skin cancer deaths. Early detection is the key. When detected early, melanoma is easily treated and highly curable, and new treatment options and surgical techniques are giving melanoma survivors more help than they have ever had before. Clinical trials are currently underway at Yale Cancer Center, Connecticut's federally designated comprehensive cancer center to test innovative new treatments for melanoma. The specialized programs of research excellence in skin cancer grants at Yale also known as the SPORE grant will help to established national guidelines on modifying behavior and on prevention as well as identification of new drug targets.

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This has been a medical minute, brought to you as a public service by the Yale Cancer Center. More information is available at yalecancercenter.org. You are listening to the WNPR Health Forum on the Connecticut Public Broadcasting Network.

- Wilson Welcome back to Yale Cancer Center Answers. This is Dr. Lynn Wilson and today we are joined by Dr. Pasquale Patrizio and we are discussing fertility and cancer. Dr. Patrizio, can you tell our listeners a little bit more about when the best time is to have a consultation with a patient who has just received a diagnosis of cancer?
- Patrizio Fertility preservation options should be discussed and explored as soon as possible, ideally at the time of the diagnosis, and most importantly, prior to cancer treatment initiation. However, it is also important to remember that we need to take care not to add additional stress to the patient and family during a very difficult time of just receiving the diagnosis of cancer. So, this has to be done with a team of experts, preferably some designated personnel and the care provider to be the union between the cancer specialist and the reproductive infertility specialist. Today, with the vast array of options that are available it is very much affordable to have a referral in 24 hours and provide some of the treatments option within a very short time frame. In the old days we were saying that we need at least six weeks to offer some options, where today the six weeks have been drastically reduced to no more than two weeks.
- Wilson On a practical level, how would a patient actually get in touch with your office or your team?
- Patrizio We do have a team of fertility preservation at Yale Cancer Center and a number of dedicated colleagues that are available for this type of referral with very short notice. We have a nurse that works in this field and we also have our social worker who is available to provide emotional counseling to both patient and most of the time together with their parents. It is really key to have a team that is available 24 x 7 just to be there when we receive a phone call from our colleagues from Yale Cancer Center and any colleagues in the New Haven area or surrounding. Then once the initial contact is made, generally we have an appointment with 24 hours and either myself or one of my colleagues will see the patient that needs immediate attention.
- Wilson Can you talk to us through what a visit is like for a patient? You mentioned a little bit about the team and the importance of that when a patient comes to the office, but who are they going to encounter first? What is it going to be like for them?
- Patrizio The first encounter is the nurse that is part of the clinical care team and after they see the nurse then they are going to see a physician, and specifically what is going to be addressed in the visit is first, what type of cancer we are dealing with, where are we in the treatment plan, what is the

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future treatment plan and does the treatment involve chemotherapy and radiotherapy, what type of chemotherapy and what type of time frame do we have? Is the chemotherapy in the future as in a week, or is the therapy going to start tomorrow? Has the cycle already started, where we are now in between cycles and so on? So, this has to first be assessed. As soon as we find out that, then we establish where the patient is in their menstrual cycle and depending on where she is in the menstrual cycle, a treatment for collecting eggs for example can be started as soon as two or three days, or at the most within a week, and then all these explanations on what the options are, are going to be entertained. If the patient is single and is young, then the option that we prefer most is to offer freezing of eggs. If the patient is in a relationship, is married, then the second option is the possibility of freezing embryos. If the patient needs any immediate treatments, in other words we do not even have the three days or four days for doing anything because the treatment has to start tomorrow or the day after tomorrow and it is a treatment that involves radiotherapy for example, then what we discuss is ovarian tissue freezing which is another option whereby we collect strips of ovarian tissue and then that ovary is going to be frozen for future use in the event the patient becomes menopausal or sterile after treatment, then she still has some fragments of ovarian tissue that can be re-transplanted back to her once she is cured from cancer. In the world, the expertise throughout Europe mostly, and in a few cases also in the United States, in St. Louis, there are now eighteen babies that have been born by doing the re-transplants of a frozen, thawed ovarian tissue for patients that did not have any time for doing the standard egg freezing or embryo freezing.

Wilson Obviously, the three main treatments that a cancer patient might be facing are surgery, chemotherapy, and radiation treatment? How does each of those treatments, specifically, affect fertility in terms of the ovaries or other reproductive organs? Obviously if we do surgery and things have to be removed that is pretty straightforward, but how does radiation play into this chemotherapy, does it have to be radiation that is specifically targeted at the pelvic area or can radiation to other parts of the body affect fertility?

Patrizio Obviously radiotherapy with beams aiming at pelvic organs is definitely very toxic for the gonads, and therefore, the recovery is very dismal. However, there are options in this case where you can transpose the ovary; you can remove the ovary from the pelvic location to higher up. However, you still have to be worried about the scattering of radiation once this treatment is performed. Next are the chemotherapies. The drugs that are used as a cocktail for treatment are much milder, much less toxic than before but still what is a problem for us in counseling is that we do not have a specific roadmap or a specific book of instructions saying if you take this particular cycle at this particular dosage, you are safe, because the same cancer in two different patients using the same exact regime of chemotherapy may produce two different results in terms of ovarian recovery

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and toxicity for the eggs. So that is the unpredictable risk, and therefore, going back to your point that radiotherapy is the most ominous, the most worrisome, followed by prolonged cycles of chemotherapy, particularly with acylating agents such as cyclophosphamide, which are known to be toxic for the very, very small eggs that are in the ovary.

Wilson: Do you see men in your practice?

Patrizio We do also see men, and it is also important for them to know that there are options for them. The most effective, most well established practice is freezing sperm, but also there are issues that need to be addressed. Sometime there is shyness, stress, and tension and it is difficult to be able to produce a sample in such conditions. However, we do have a team that will talk to the patient and try to make them more at ease. We have a room just for collection and sometimes we have to go to the hospital to do collection because they are too sick. Sometimes they really cannot do it and then we still have the option of waiting for a cycle or two of chemo before we offer it again. Now of course there is the possibility of recovery of sperm production and ovarian function. For ovarian function we still want to see these patients because they need to be told that they are at risk for premature menopause, in other words, they may cease the ovarian function early because they underwent chemotherapy. For men, when they recuperate their sperm function, and they still have sperm frozen, three or four years after that fact, it is safe to say we can discard those samples that we have frozen, because now that sperm function is back.

Wilson A question that often comes up is after a patient has gone through a successful cancer treatment program, male or female, if they are interested in becoming pregnant or having a child, when it is really safe for them to try to do that?

Patrizio We have this concept of waiting six months after chemotherapy for both men and women if there is resumption of sperm or resumption of ovarian function after a washout time of six months then she should be fine, but you also have to be careful, particularly for some patients with breast cancer, a pregnancy has to be considered in the realm of what type of cancer were they originally diagnosed with? Was it an estrogen positive receptor cancer? Was it progesterone receptor positive, or HER positive? This all has to be discussed in the context of a team with the oncologist and having the okay for that particular patient after a period of time. Usually with breast cancer, as you know, they undergo a treatment for about five years of tamoxifen, or depending on the stage when the cancer was diagnosed, they may stop after two years or three years to give them a chance to have a pregnancy, or perhaps we need to change the regime and not use tamoxifen and use letrozole, which is an aromatase inhibitor, but we do talk a lot with our colleagues here at Yale so it is a multi-disciplinary decision that benefits the patient and also their family.

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- Wilson You had mentioned several options for women, could you review those in some more detail? There are various procedures, but what is it actually like for a patient? Is the procedure done in the office? Do they need to be in the hospital or spend the night? Can you talk us through some other more commonly performed procedures?
- Patrizio The procedures that are performed in the office are egg freezing or embryo freezing. The embryo freezing is the most established one. It is non experimental, but egg freezing in the United States is still considered experimental. These are the two most commonly used options. Next to that is the option of doing a laparoscopic surgery whereby we obtain fragments of cortical pieces of the ovary, so this requires a patient to undergo anesthesia, and we need to do a surgical intervention to collect the ovarian tissue that is going to be frozen. And this is also considered experimental, so the established embryo freezing, and experimental egg freezing, or ovarian tissue freezing. Now there are some other options that are on the horizon. Other options are, for example, if the patient does not have time to be stimulated with the medications to produce eggs but when we see the ovary on the ultrasound we can see that there are small follicles, which means they may have a harvest of those small follicles and we can get immature eggs, and today we are able to mature those eggs in the laboratory. So, this is a nonsurgical process. We aspirates the small follicle, we aspirate those immature eggs, and the patient can benefit from some of them being mature and then they can be frozen, all can be fertilized for embryo freezing. In the pipeline, and I want to make this comment because it is important for our research that our patients understand and that the public understands that there are some cancers where we really do not have much time, for example, leukemia. For a patient with the leukemia, when we receive the phone call they are already sick with high fever and debilitated and the only option for them is take a piece of ovarian tissue; however, as you know, leukemia is also a cancer that spreads all around the body and goes also to the ovary. So now if I do an ovarian tissue harvest, then I cannot re-transplant the tissue back to the patient when she is healed, because I may have a very high risk of transmitting back the cancer to that patient that is now healed. So what we are doing at Yale, and also at other centers, is what we call in vitro follicular genesis, in other words, we are trying to stimulate the growth of eggs from these ovarian pieces while the tissue is in the dish, in the laboratory, and that is where we are hoping to make some strides. Other research that we would like to continue and we are implementing a few more steps for now is whole ovary freezing and whole ovary perfusion. In other words, if I take an entire ovary and I can attach this ovary to a peristaltic pump in the lab, I could theoretically keep this ovary alive for x number of days, and if there are leukemia cells, I am not going to transplant this ovary. I am just going to produce eggs in vitro, and then I can just discard the tissue.

Dr. Pasquale Patrizio is Professor of Obstetrics, Gynecology, and Reproductive Sciences at the Yale School of Medicine and Director of the Yale Fertility Center. If you have questions or would like add your comments, visit yalecancercenter.org, where you can also get the podcast and find written transcripts of past programs. You are listening to the WNPR Health Forum on the Connecticut Public Broadcasting Network.