



Minimally Invasive Techniques to Treat Cancer

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Welcome to Yale Cancer Answers with Drs. Anees Chagpar and Steven Gore. I am Bruce Barber. Yale Cancer Answers is our way of providing you with the most up-to-date information on cancer care by welcoming oncologists and specialists who are on the forefront of the battle to fight cancer. This week, Dr. Chagpar is joined by Dr. Raj Ayyagari for a conversation about interventional radiology and minimally invasive surgery. Dr. Ayyagari is assistant professor of Radiology and Biomedical Imaging at Yale School of Medicine and Dr. Chagpar is Assistant Director of Global Oncology at the Yale Comprehensive Cancer Center.

Chagpar Raj, we talk about radiology and most people think about radiology as being x-rays, like chest x-ray or CAT scan. What is interventional radiology?

Ayyagari Interventional radiology is basically image-guided minimally invasive surgery. We do lots of things related to cancer where we go into the arteries; we will do procedures under x-ray, CAT scan, or ultrasound guidance. We will go into the blood vessels, the arteries, the veins, will go to cancers, various tumors. We will do something called embolization where we will inject these little beads that may be coated with a chemotherapy drug or radioactive substance that can treat tumors in a minimally invasive and often outpatient approach without any big incisions or scars. We also do a lot of other things. We stop bleeding when patients come in with a trauma, splenic or pelvic trauma. We do lots of opening up of vessels and restoring blood flow, so angioplasty stents, things like that. We also do a lot of other nonvascular work, biopsies, drainages, putting tubes in obstructed kidneys, obstructed gallbladder, and obstructed livers things like that.

Chagpar It sounds like you use x-rays to guide interventions?

Ayyagari Correct, x-rays, CAT scans, and ultrasounds, all sorts of imaging modalities.

Chagpar It is really interesting when you started off talking about very minimally invasive surgery because a lot of us think about surgery as a big deal, right, like somebody is taking a knife and opening you up and often trying to get cancer out. So how do you that in a minimally invasive way with x-rays?

Ayyagari Basically, if we are doing a procedure where we go through someone's arteries, for example, we will put a small little hole, maybe 2 or 3 mm into the artery and through that we will thread a little catheter that you can see under x-ray imaging and then we will use that imaging to kind of guide the catheter into the blood vessels into the tumor, and we will inject dye, map out the blood vessels, find our way into, for example, a liver tumor, and then we will inject lots of little beads, either coated with like I said drugs or sometimes radioactive substances and those

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beads will kind of float in, cut off the blood flow to the tumor and then the drug can be released from the bead and treat the tumor. We can do this on an outpatient basis essentially. We then take the catheter out, put a little bandage on the patient and then if they stay overnight or go home the same day, the post-procedure course is much more abbreviated, the recovery time is much shorter than if someone has an actual incision.

Chagpar Are patients awake when you do this or is this under an anesthetic?

Ayyagari Typically they will get moderate sedation medication, something akin to what they might get when they get a colonoscopy or an endoscopy.

Chagpar And so is it just as good as if you have, so you were talking about a liver cancer, is it just as good to have you put in this fine little catheter and these little beads that have chemotherapy and/or radioactive substances, as actually having the liver tumor resected or do you do that only when you can't resect something?

Ayyagari It depends on the size of the tumor and other technology, which is called ablation where we use ultrasound or CAT scan guidance to put a small needle through the skin into the tumor and then actually just burn it or sometimes we can freeze them as well. For that technology, again it is through a small hole, the patient goes home typically the same day. In the liver, for tumors smaller than 3 cm, if we cover it well, the 10-year survival and disease-free recurrence rates are basically equivalent to surgery. Now, when we talk about the embolization, that is not the same as a total complete cure for tumors, we are usually doing what we can to kind of keep the tumor under control for as long as possible. There are certainly different candidates for different procedures and generally, for liver cancer, for example, if they can be ablated or surgically removed, that is the standard of therapy, but there are lots and lots of patients who don't fall into that category of health that can withstand a big surgery like that and so for them, the embolization is a good procedure.

Chagpar The ablation is where you go in and you essentially either fry the tumor or you freeze the tumor or something to make the tumor evaporate, but that is done with a small needle too and so that is better than embolization which is where you kind of inject these beads and cut-off the blood supply. So who would not be a candidate for ablation because it seems like if ablation is better, everybody should opt for ablation instead of embolization.

Ayyagari Right, so tumors that are bigger than 3 cm, especially over 4 cm in diameter can be really difficult to ablate thoroughly, because it is too big to kind of put in enough heat to treat it. Someone has 5 or 6 tumors, you can imagine, burning holes all over the place might be a lot for the patient to handle or if someone has diffuse disease throughout an organ, the liver for example, then the ablation is for a focal tumor or a few tumors that are of certain size.

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- Chagpar Got it. So is it that these techniques only work in certain organs, for example, many patients have breast cancer, and yet, we really do not hear about these kinds of interventional radiology procedures for breast cancer.
- Ayyagari Yes, that is a great question. I was talking about it with my wife yesterday. These technologies have been proven and have a long track record in organs like the liver, the kidneys, actually the prostate and in certain circumstances, the uterus. Now, we do it also for lung tumors sometimes. Breast tumors, it is something that one would think would lend itself to this kind of technology, but there are not a lot of data out there and not a lot of people who have actually tried it. I know you have expertise in that, maybe you can tell me more about that. I actually am very uninformed in that area of the body in terms of what is available, but I would love to see it happen and I have heard of studies where this technology is applied, but today there is really nothing out there in this kind of modality for that kind of cancer.
- Chagpar In breast cancer, people have tried ablation, they have tried ablation with cryotherapy where we freeze the tumor, they have tried radiofrequency ablation, they have tried it with high frequency ultrasound, they have tried it with laser and the issue really is that you don't get a 100% kill rate and the imaging is such that even though it looks like it is completely cooked, it might not be and the issue too is that breast cancer surgery is so well tolerated and most women are so amenable to it and can be done as an outpatient and so on and so forth, it isn't one of those organs like the liver where you've got big blood vessels and tumors can be in awkward spots that are difficult to surgically resect where ablation with interventional radiology is particularly helpful. So you mentioned a few other organs where interventional radiology really plays a key-role in terms of management of cancer. Can you tell us more about that?
- Ayyagari In cancer, per se, livers are the main organ. We will also work a lot in the kidney. We will do more percutaneous ablations, particularly cryoablation in that realm. So patients with tumors that are small enough to ablate and at this point, you know the way that the data play out, the resection is small, partial resection of the kidney ends up still being the gold standard of care, but for tumors that are small and for patients who are not the best candidates for surgery, we can do these ablations and again, it is usually cryoablation of the kidney. However, I think that the 10-year-data are approaching the quality of that for a partial nephrectomy and I think as decades go by and the technology gets better and better and experience gets more and more complete, hopefully we will get to the point where we can offer an equivalent rate of disease-free survival and recurrence.
- Chagpar And it is nice, especially if you've got a tumor in an area of the kidney where you would have to resect the whole kidney just because of the way the kidney works and its anatomy. When

you can ablate that and leave the rest of the kidney function, just like you leave the rest of the liver function, that is nice, so that is another difference with breast, it is not really like you are losing function in this solid organ. Tell me about other organs, you mentioned that kidney and liver are really your main sources for cancer, but are there other sites on the horizon that you are looking to move into?

Ayyagari Absolutely. We have been doing a lot of embolization procedures in the prostate gland in men and so, right now, we do this for benign prostatic hypertrophy, and as we grow older and older the prostate gets bigger and bigger and the large majority of men suffer from BPH as they get older and so for lots of men, the medications that are out there help open things up and let your inflow and people do quite well with those, but there are side effects with those medications and at some point, they stop being as effective as one would like and so then, the patient starts considering a procedure to have that channel opened up again. Again, the gold standard of therapy currently is what is called a TURP, a transurethral resection of prostate, basically, a surgical procedure under general anesthesia where the urologist places a rigid endoscope up the penis through the urethra and then they basically kind of shave off, use lasers to kind of open up that channel. It works very well, again it is the gold standard of therapy, but probably for those out there listening, the description of the procedure tends to curl a lot of toes when you are describing the invasiveness of it and there are lots of side effects, the recovery can be tough with it. One of the side effects is retrograde ejaculation where more than half of men will not be able to have a normal sexual function afterwards. So something we have been doing now for about 6 or 7 years, is applying these embolization techniques that we have been doing for decades in other organs and kind of applying those to the prostate gland and actually, I just had a procedure this morning where again the patient comes in, it is an outpatient procedure, we go through a tiny little hole in the artery, the catheter all the way down to the arteries that feed the prostate, will inject these beads and then take everything out. The procedure lasts 2 or 3 hours. Some people even do it faster and then, the patient goes home after a few hours of recovery and usually within a few weeks and definitely by a month, they have noticed a substantial improvement in their flow and by about 3 or 4 months, the gland slowly shrinks over that time and they do really well. Probably about 9/10 patients have great results and the results are almost as equivalent as the TURP surgery in terms of the amount of symptom improvement and the improvement of the flow. Right now, it is still not an FDA-approved procedure it is technically experimental, but we have been using these beads and these techniques and this medical reasoning in other parts of the body for decades and so for example, we do it for uterine fibroids in women and we have been doing that for about 25 years. So applying the anatomy, the technology, the physiology, the pathology to this just seems like it is going to work really well. We now are getting 5-6-7 year data on this procedure and the results are fantastic. So we are hoping as time goes by, it will prove itself to be a mainstay of therapy for BPH, but you asked how this may relate to cancer

and so, now obviously we talked about these embolization and ablation procedures we do for other organs and so we hope that somewhere along the line, we will be able to start doing perhaps a chemoembolization for prostate cancer or radioembolization for prostate cancer and there have been 1 or 2 studies out that have kind of started exploring that already, so that is in the pipeline.

Chagpar Great. I cannot wait to learn more about how embolization and ablation are really going to help revolutionize cancer care, but first we need to take a short medical minute. Stay tuned to learn more information about interventional radiology with my guest, Dr. Raj Ayyagari.

Medical Minute

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The American Cancer Society estimates that there will be over 75,000 new cases of melanoma in the US this year with over 1000 of these patients living in Connecticut. While melanoma accounts for only about 4% of skin cancer cases, it causes the most skin cancer deaths. When detected early however, melanoma is easily treated and highly curable. Clinical trials are currently underway at federally designated comprehensive cancer centers such as Yale Cancer Center and at Smilow Cancer Hospital to test innovative new treatments for melanoma. The goal of the specialized programs of research excellence in skin cancer or SPORE is to better understand the biology of skin cancer with a focus on discovering targets that will lead to improve diagnosis and treatment. This has been a medical minute brought to you as a public service by Yale Cancer Center and Smilow Cancer Hospital. More information is available at YaleCancerCenter.org.

Chagpar This is Dr. Anees Chagpar and I am joined tonight by my guest, Dr. Raj Ayyagari. We are talking about interventional radiology and right before the break, Raj was telling us about some cool new technologies. Well, they are actually not that new, but really cool, in the sense that they can now take a little catheter, put it in through your left wrist, drain a little catheter all the way down to your prostate and for the men out there who have large prostates, they can embolize or actually put in little beads that disrupt the blood flow to the prostate such that the prostate shrinks and you have good urine flow again, which is a really cool concept and while still experimental, it is something that they have been using at Yale for a while and I had asked Raj right before the break about how this applies to cancer. So Raj, is this going to be something where we take beads similar to what you were talking about in the liver that are coated with some kind of chemotherapy or some kind of radioactive substance, such that for men who

maybe either can't have a surgical procedure or don't want to have a surgical procedure because of all of the potential side effects that they can then do this to eliminate cancer or alternatively that they can do this instead of this watchful waiting?

Ayyagari That is a great question. As you just mentioned, the watchful waiting, prostate cancer treatment generally falls into kind of 2 large categories, the patients who are with disease severe enough and they are healthy enough to go for a curative treatment be that surgical resection or a focal ablation or radiation therapy in certain cases and there are lots of patients on the other end of the scale who have cancers that have spread behind the gland or just not able to get a cure and they are in the kind of palliative treatment category, but there are a lot of patients that fall in between those 2 categories, healthy men, maybe with low grade disease or not so healthy men with moderate grade disease and lots of prostate cancers are generally indolent and if you look at autopsy studies where people just looked at an 80-year-old man who died for whatever reason, they look through the prostate glands and probably almost 80% of them have cancer, so prostate cancer can be a very kind of slow growing indolent thing, so a lot of urologists have tried to kind of not over treat prostate cancer. A lot of patients out there probably do not need to be treated so aggressively and so there is this whole concept of watchful waiting and trying to put patients into different categories so that we can avoid over treating them and exposing them to unnecessary risks. So when we apply what we talked about with the liver treatments, it is local regional therapy that includes embolization with chemotherapy, embolization with radiation, and also ablation. We begin to wonder whether we can apply this model to the prostate gland as well. We have been seeing that the prostate gland really tolerates incredibly well having its blood flow shut down. We have been doing this embolization procedure for BPH now for 6 or 7 years and patients tolerate it wonderfully. Then we begin to ask well for these people with prostate cancers can we inject the beads that are coated with chemotherapy or theoretically the radiation and so there are a couple of studies out there that have been going on and come out with some data this year exploring that possibility. Obviously, there is a long way to go before we can claim this as a really safe and proven treatment for prostate cancer and there are a couple of technical issues that may make it a little more challenging to treat. Usually prostate cancers pop up on the very outer edge of the gland whereas with this embolization procedure for the BPH, we are more affecting the center core of the gland, but that said, there is a lot of promise in this procedure and its application for cancer. So that is coming in the next few years. We also talk about doing ablation of the liver or the kidney. There are now ways and techniques and technology to do these ablations in the prostate as well. We are developing at Yale actually MR-guided percutaneous biopsies and ablations of focal prostate cancer, again for patients who may not be candidates for surgery or may not wish to go through the surgery, so that is something we are actively developing now and really there is only, I guess, one other institution in the country that is doing percutaneous MR-guided biopsies and ablation of the prostate. The

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prostate gland is a very difficult organ to image. An MRI is generally the imaging modality of choice and so that is what we would like to use to guide our interventions as well. So yeah, when we applied this kind of this whole liver therapy kind of paradigm to prostate cancer, it really opens up a lot of exciting pathways for future treatments.

Chagpar And so one question though, I remember on previous shows that we had when we were talking about prostate cancer, our guest kind of said that usually if they are going to do a biopsy, it is often a random biopsy in most centers which made me think that prostate cancer was more ubiquitous through the gland whereas ablation is a focal like, I see the lesion, let me ablate it, so how does that work, is it really that prostate cancer is focal, but we just have poor imaging or is it that it is more glandular disease that affects the whole gland and somehow, we are going to try to ablate the whole gland?

Ayyagari It is kind of in between, but probably more towards the former part of that so, prostate cancer, the way we see it, the way we image it on MRI is typically a focal disease, 1 or 2 or 3 or maybe 4 spots that light up. The problem is prior to at least the past decade if not less, we never really had good ways to image the prostate. Prostate MRI really cannot image small tumors well. Prior to that technology, literally the biopsies were random, we would hope that our urologist would biopsy the entire gland and hope that they caught, you know, the one or two smaller tumors. Now, that said, the cancer, we know for a fact that the cancers that we see on MRI are bigger than what we see and probably the same as prior, but with most cancers that the imaging is underestimating the size of the tumor, but that said, tumors that we can see that merit treatment are usually kind of worth going after whereas a lot of people speculate that spots of cancer that show up on imaging may be the cancer that we do not even need to bother treatment.

Chagpar Yeah, that is too indolent.

Ayyagari We do think of it as a focal disease and when we talk about ablations or biopsies, we would like to be very focal. Again, the technology is just coming into creation in the past few years and so here at Yale, there is a group led by Dr. Preston Sprenkle, who is a urologist, who does fusion biopsy. So we will get an MRI of the patient's prostate that will show us where there are a couple spots that are highly suspicious and then he will bring the patient in and put an ultrasound probe in the rectum of the patient and fuse those images with the MRI and then do what is called a transrectal biopsy which is how the random biopsies were done, but now they are being done with more imaging guidance and that fusion biopsy is proven to be a fantastic way to kind of increase the yield for biopsies and so, then some urologists take that same technology and in the operating room, will do ablations where they use fusion imaging, the MRI, to help show where the tumors are, the ultrasound in the operating room to guide the ablation probe placement. We are now developing technology to do that all and the MRI scan

away from the operating room and avoiding you know putting things in the rectum, because that can increase the risk for infection. So that is where we stand with that, but if it is a focal cancer, I think generally speaking, and one at least that we would like to treat focally.

Chagpar And so the other disease site that you mentioned for uterine fibroids where you have used this for a benign disease, but we know that women get uterine cancer too, is there a potential that just in the same way that you are moving embolization of the prostate potentially into treating prostate cancer that this could be used in uterine cancer?

Ayyagari That is another great question, so probably not, and I may not be the best person to talk about the science behind this, but we know for a fact that there are lots of organs in the body where we would love to be able to embolize tumors and get good treatments, but the technology just does not work, for example in the lung and in the kidney and also as you asked about in the uterus. Those types of cancers for whatever reasons they just seem to their tumor biology is different, they are not so encapsulated, so limited in their blood supply to very focal vessels and so the tissue spread, I guess a lot of has to do with the blood flow and the cancer can spread behind areas that are supplied by one artery or another and so going into emboli, say a renal tumor has been shown to not be very helpful at all and unfortunately, in uterine cancer, the situation is probably even worse. Uterine, cervical cancer, gynecological malignancies generally just don't lend themselves to being treated by embolization procedures.

Chagpar What about ablation, I mean we know that in cervical dysplasia, high-grade dysplasia, they often like freeze the cervix, so could we use that same kind of thinking to ablate uterine cancer?

Ayyagari I think it will be tough. I think they are hard to image and so when they are doing cervical ablation it is usually under direct visualization because they can see where they want to treat. If we are doing something for the uterus or uterine tumor, we depend on imaging to kind of guide us typically unless we are opening a patient up in the operating room and the imaging of such cancers can be very, very difficult to definitively localize them. Likewise, there are lot of other organs in the abdomen and pelvis right adjacent to the uterus and one has to be careful about damaging those organs and that can be tough. In cervix, you have kind of error, a lot more I would guess, but in the uterus not so much.

Chagpar Right. The other place where I think interventional radiology really plays a huge role is trying to get cancers that we can't get at well as surgeons, particularly because they are in tight spots or they are near important structures that are at risk or that if were to torque that would lead to side effects, so very similar to what we were talking about in terms of the liver and the prostate and so one of the areas that I think about is the brain and brain metastasis. Is there a role for interventional radiology in ablation of brain metastasis?

Ayyagari I actually do almost nothing intracranially, so I don't have any experience or much authority on the topic, but I will say again, imaging is the challenge there and obviously, the stakes are much higher if you are in the brain. If you are in the kidney and you ablate a little bit of the normal tissue, you know, no big deal. Obviously, in the brain, that is not the case. Also, getting in through the skull, that requires drilling a hole versus just putting a needle through the skin to get to other organs. So I think doing something percutaneous like an ablation or an embolization is not really feasible in terms of intracranial problems, but there are a lot of things called, for example gamma knife, where radiation oncologists can actually focus a radiation beam to be more focal and not surgical, I guess you know using the term loosely, but yeah in terms of what we can offer as interventional radiologists intracranially, we just don't have much to offer for cancers.

Chagpar And so it is interesting because all of the different specialties kind of have their own little bit that they are very good at.

Ayyagari In my experience the collaboration has been fantastic. In fact, when I started working here, a friend of mine who is a urologist came to me and said hey I heard about this thing, prostate artery embolization, can you start it up here at Yale and I said yeah, sure, I would love to. So I just kind of looked into it and then gave a presentation about it and they started referring patients and the first patient did great and the urologists will say nothing beats the grin on the guy's face when they walk in a month after and they can urinate again. I think they really recognized the value of what we can offer and want to do what is best for the patient and so it has been a great collaboration.

Dr. Raj Ayyagari is Assistant Professor of Radiology and Biomedical Imaging at Yale School of Medicine. If you have questions, the address is canceranswers@yale.edu and past editions of the program are available in audio and written form at YaleCancerCenter.org. I am Bruce Barber reminding you to tune in each week to learn more about the fight against cancer here on WNPR, Connecticut's Public Media Source for news and ideas.