



Colorectal Cancer

Colorectal Cancer Awareness Month: Radiation Therapy

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Welcome to Yale Cancer Answers with doctors Anees Chagpar, Susan Higgins and Steven Gore. I am Bruce Barber. Yale Cancer Center 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. March is colorectal cancer awareness month and this week our guest host, Dr. Howard Hochster welcomes Dr. Kimberly Johung. Dr. Hochster is a Professor of Medicine in Medical Oncology, Associate Director for Clinical Sciences at Yale Cancer Center and an expert in Gastrointestinal Cancers. Dr. Johung is Assistant Professor of Therapeutic Radiology and Director of Gastrointestinal Radiotherapy Program at Yale School of Medicine. Here is Dr. Howard Hochster.

Hochster Dr. Johung, can you tell us a little bit about what radiation is and how we use it for treating colorectal cancer?

Johung Sure, radiation therapy is the use of high energy radiation to try to kill cancer cells. How it works is that it damages cancer cell DNA which they rely on to divide and grow. They damage so much that the next time they try to divide they die off instead. This radiation is delivered typically from a machine that is called a linear accelerator which focuses high-energy x-rays towards the patient's tumor from outside the body. We can also actually place radiation sources within the tumor which can be used to directly damage cancer cells.

Hochster A lot of people think that when you get radiation, you have a lot of problems related to the region as skin toxicity, really kind of burns or damages normal cells, is that true today still?

Johung I think it is a hard thing for a patient to sign up for when they have been told their whole life that they should avoid exposure to radiation. The difference is that we have technology used to really focus that dose of radiation to the target which is the tumor and try to avoid dose to normal tissues so that we can minimize side effects in that way.

Hochster So, the current technology, the linear accelerator machines, they are lot different than the early days of radiation.

Johung Exactly, so I would say that in the early days of radiation, we were really aiming large, open wide beams towards patients and that would mean that essentially all of the tissue in the way would get treated in addition to the tumor, you would be treating normal skin, normal bowel, normal bladder. The difference today is that we are able to

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shape that radiation dose better. There are technologies such as something called intensity modulated radiation which really is a way that allows us to carve the radiation dose. You are no longer send doses of large box towards your tumor target, but you are able to determine exactly where that should be deposited and sharply carve that dose away from nearby structures.

Hochster And also the linear accelerator type machines are higher energy, so they tend to go through the skin and so forth and not affect as much.

Johung Exactly right.

Hochster So it is that plus this computerized planning and some of these other more fancy techniques that allows the radiation to be concentrated where the bad cells are pass through the good cells without damaging them.

Johung And you know, a similar advance would be something that we call image-guided radiation therapy, so you can imagine that on a day-to-day basis when a patient comes for radiation treatments, their body is in a slightly different position or perhaps the internal organs are slightly in a different position and in order to take that into account, we have to treat the tumor target with a larger margin. With image guidance, we basically can obtain x-rays or even CAT scans every day on the treatment table which allows us to position the patient more accurately and therefore reduce the treatment field.

Hochster That is very hopeful that we will be able to get more of the radiation where it really needs to be.

Johung Put it where it is supposed to be and avoid the normal tissue that is really the goal of the treatment and that is how we minimize toxicity.

Hochster Yeah, so in colorectal cancer treatment today, we do not use radiation for most of the people with colon cancer certainly, how are we using it today?

Johung Right, so as you just mentioned, colon cancer is typically managed without radiation therapy based off of many studies that really show there was no benefit to adding that because surgery is so effective, so radiation is typically used to treat rectal cancers which lie lower in the pelvis. Because of that position, it makes surgery more challenging if you will and so we typically treat all rectal tumors that are stage II or stage III. This means that the tumor is large enough in the pelvis or has spread to nearby lymph nodes in the pelvis such that if you proceeded with surgery alone, there is a high risk that the tumor grows back in the pelvis after surgery, so we know that

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there is a benefit to shrinking the tumor or reducing the burden of tumor in lymph nodes prior to surgery in terms of reducing the risk that cancer can grow back after a surgical procedure.

Hochster So, if I have colon cancer, I usually will not get radiation and if I have rectal cancer, that is kind of in this intermediate stage, I probably will get radiation.

Johung Exactly.

Hochster And how do I tell if it is colon or rectal cancer? I mean I know I can ask my surgeon but besides that?

Johung Rectal cancer is defined as basically being lower in the pelvis, so it is anywhere from the anus up to usually about 12 to 15 cm distance and that is measured typically by a gastroenterologist who is doing a colonoscopy and would diagnose the tumor and see where it is located in the bowel.

Hochster So, the last 5 to 6 inches of the colon is the rectum.

Johung If you subtract out the distance of the anus, exactly. We can often rely also on CAT scans and MRIs and just looking radiographically where that is positioned in your body.

Hochster Biologically is there a difference between what is in the rectum and what is in the rest of the colon?

Johung I think that it is more an issue of local control being challenging in the pelvis because of anatomic location.

Hochster So it is just harder to get in there are operate and get everything out as easily?

Johung Exactly.

Hochster But surgeons have changed their approach a little bit.

Johung Right, surgeons have changed their approach in the sense that the surgery is a more extensive surgery, basically, not just taking the tumor tissue but really taking all the surrounding tissue out to the sides of the pelvis and that has minimized risks of local recurrence, but even in that setting, there have been studies showing that adding on radiation continues to provide a local control benefit in terms of reducing the risk but that tumor can grow back.

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- Hochster So, for rectal cancer, because the surgery is not quite as effective at controlling it locally, we add the radiation for rectal cancer.
- Johung Agreed.
- Hochster And even with the better surgical techniques, we still can use radiation and still reduce the risk of some cells being left behind and growing back in the pelvis.
- Johung Right and certainly there is probably also biologic differences between how a rectal cancer behaves and how a colon cancer behaves, that also contributes to this local control being more meaningful.
- Hochster So what is involved if somebody needs rectal radiation?
- Johung Typically we start with the basic consultation, that is really just meeting and discussing why radiation therapy would be beneficial and what those expected side effects would be. Often times, patients are most surprised by the fact that radiation is delivered with daily treatments and they have to come for dose of radiation, Monday through Friday, for a course that is typically about 5-1/2 weeks. The reason for that is that a little dose of radiation every day causes enough injury to the tumor cells to have them die off but that your normal tissue surrounding the tumor can heal in between each of those daily doses, so the first step for planning radiation would be a special CAT scan, we call it a CAT scan simulation but really what that is is positioning your body in the way it would be for treatment, obtaining a CAT scan that we can generate a treatment plan off of and we then embark on the radiation treatments within a week or so.
- Hochster And the treatment plan is basically a computerized way of delivering the radiation in doses to a defined field.
- Johung Right, treatment planning is something that actually we as radiation oncologists spend much of our time doing. It has become a lot more intricate than it was in the past. We had talked about some of the advances in treatment delivery from the days many years ago with much wider radiation fields where really planning was done on a 2-dimensional x-ray. Nowadays, with the CAT scan images that we obtain, we have slices through the pelvis every 2 mm and we really are defining what the tumor target is at every slice as well as what the normal tissues are that we want to avoid and our job as physicians is to identify those volumes and then we work along with the physics team to help generate the best plan which really is what energy of radiation are we using,

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How are we shaping the fields, how are we modulating the intensity of those fields, which angles should they come from and all of that to help maximize tumor delivery of radiation and minimize dose delivery to other tissues.

Hochster Because you can shape the fields with closer edges and so forth, I mean what are some of the side effects that you avoid compared to other older forms of radiation for the rectum?

Johung Right, so in this particular area, the main side effects that we are concerned about are injury to the normal bowel which can result in diarrhea or nausea or changes in appetite, also doses to the bladder which can cause some frequency of urination and then we have talked earlier about toxicity to the skin which can end up being like a severe sunburn type of reaction, so probably the best evidence that are newer techniques of radiation can reduce these toxicities is actually in the treatment of anal cancer where we have good data comparing simpler radiation plans to these more refined approaches and follow those patients and show that their skin toxicity, their GI toxicity and their bladder toxicities are less with these treatments.

Hochster And besides the bladder toxicity, then there are also issues for men with erectile dysfunction, we see that very often today with rectal cancer radiation.

Johung Right, so with the use of these techniques, we are able to minimize dose you know to those nerve bundles and also minimize risk for infertility. We are treating a lot of younger patients nowadays with rectal cancers and a dose to the testicles for example, could lead to issues with infertility that can be minimized with these types of techniques.

Hochster And the ovaries for women.

Johung Exactly, we cannot forget about the women.

Hochster Right, so that is all really major progress. You know when we started out giving treatment for colon or rectal cancer, it always started with surgery and then we gave chemotherapy and radiation for rectal cancer afterwards, but there were some long-term side effects of giving radiation after, so now we have pretty much gone to doing radiation preoperatively, can you tell us a little bit about that.

Johung So we know that giving the radiation prior to surgery as you said, is more effective. It also minimizes the toxicity compared to receiving that radiation after surgery and really there are 2 reasons, I think that if you are treating the tumor before it is removed, you know exactly what you are targeting, whereas if you are trying to treat the space that the tumor was in after it was removed, that generally is a larger area meaning that you

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are treating a lot more normal tissue. The other challenge is that once the tumor is removed then a lot of normal tissue falls into the space where the tumor was, so again we end up irradiating more normal tissue. We are also a lot of effective at treating something you can see and so that is where the increased local control benefit of treating prior to surgery comes from.

Hochster And does it help the surgeons?

Johung Well, it does help surgeons in the sense that if you are reducing you know the volume and the burden of tumor and what it might be stuck down to, then often times creating a wall of fibrosis or scar tissue between the tumor and adjacent blood vessels, for example, can make dissection of that tumor away from those structures much easier. The surgeons might argue that the fibrosis makes surgery more challenging.

Hochster What about if it is low down close to the anal muscles, and sometimes, we have to worry about you know are they going to have good sphincter function, will they need a bag, radiation is helpful in that too, right from the trials that have been done.

Johung Certainly, you bring up a good point which is that often times when tumors lie very low in the rectum in order to remove them, there is not enough bowel left to reconnect the colon, so therefore, those patients end up having a permanent bag for their stool. We know from some of the trials that in patients where you think their tumor is so low that they will require that type of surgery if we embark on radiation to minimize the tumor size prior to surgery about at least 40% of them are converted from what we thought would be a surgery requiring permanent colostomy to the one where they do not need that procedure.

Hochster Well, thank you, we are going to take a short break for a medical minute, please stay tuned to learn more information about the role of radiation therapy and colon cancer with Dr. Kimberly Johung.

*Medical
Minute*

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There are over 13 million cancer survivors in the US and over 100,000 here in Connecticut. Completing treatment for cancer is a very exciting milestone but cancer and its treatment can be a life changing experience. Following treatment, the return to normal activities and relationships may be difficult and cancer survivors may face other

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long-term side effects of cancer including heart problems, osteoporosis, fertility issues and an increased risk of second cancers. Resources for cancer survivors are available at federally designated comprehensive cancer centers such as the one at Yale Cancer Center at Smilow Cancer Hospital to keep cancer survivors well and focused on healthy living. More information is available at YaleCancerCenter.org. You are listening to WNPR Connecticut's Public Media Source for news and ideas.

- Hochster Welcome back to Yale Cancer Answers. This is Dr. Howard Hochster and I am joined tonight by my guest, Dr. Kimberly Johung and we are discussing radiation and colon cancer. So Kim, we were just talking about how preoperative radiation has changed a lot of long-term side effects of radiation when it is given after surgery and might make the surgery more easy for the surgeon and it also can help in some cases where the tumors are low allow more room to connect the colon and the rectum together, so you do not need a colostomy, so what are still some of the long-term side effects of radiation or are they you know what percent of people have these and what do we worry about that?
- Johung So I think what we worry about in terms of long-term toxicities are mostly late bowel toxicities. This can include basically strictures at the anastomosis which really means that the area where you bowel is reconnected becomes scarred down or that you could have obstructions elsewhere in your bowel and you know these are now rare with the techniques that we have but at their worst, would require surgical intervention for repair and so I think that you know all these efforts we make to avoid giving radiation dose to tissues that are not you know do not need to be treated are very important.
- Hochster And is that very common today using when the later series with more current techniques, how frequent are these kind of late side effects?
- Johung Right, so I think that when we give radiation in the preoperative setting versus in the postoperative setting, we already see a reduction in late toxicity, so that it is in the single digits range, you know, under 10% and so while we do not have numbers for late toxicities with intensity modulated radiation for rectal cancer for example, you know, these numbers are even lower, so probably you know between 5% and 10% risk.
- Hochster So most of the time people are not going to have too much in the way of skin toxicity, maybe a little diarrhea, maybe a little bladder irritation, but mostly the radiation goes pretty well.

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- Johung Right and often times we have patients who are able to continue their full time work during treatment and so you know the biggest annoyance is having to stop by our department every day for a treatment, but you know their toxicities are managed quite well, so that they can continue to function in their life as they had you know off treatment.
- Hochster So some people, specifically people in Scandinavia, are looking at different schedules of radiation, so you do not have to come so many times. There is like one program that uses like five doses of preoperative radiation and do you use that here and what are the pros and cons of that?
- Johung Right, there are Dutch and Swedish studies looking at this, which is basically using larger doses of radiation and just five treatments rather than this protracted course that we have been talking about. Benefits are, one, that you are not needing to come for so many treatments, you get on to the definitive therapy which is surgery sooner and really have this work as it if you give the radiation in a larger dose, you are getting a larger biologic effect of it on the tumor, so we do this without chemotherapy when we are giving radiation slowly over the course of five weeks, we rely on chemotherapy as a radiosensitizer to make that treatment more effective, so when we are doing larger doses, this would be five treatments in the absence of chemotherapy. The data actually shows that the outcomes in terms of local control of the tumor are probably equivalent with some concern that if you have tumors that are lying lower in the pelvis that perhaps that standard course of five weeks of treatment is more effective. So probably this has not come into practice here in the United States merely because of practice patterns and this is more commonly used in Europe where the studies were done.
- Hochster We have an organization that Yale is part of that can set standards for medical practice and insurance called NCCN in the rectal group we have set that as an alternative today for radiation besides the long course, the five-day course, you agree with that? That should be an option.
- Johung Absolutely, I think in my practice I have certainly considered this treatment, particularly for patients where because of their social situation it would be very challenging to come for daily treatments and you know another scenario where the patient who may not necessarily be felt to medically be able to tolerate chemotherapy along with radiation and so therefore rather than doing five weeks of radiation alone, the treatment will probably be more effective if we deliver this in the European style, five treatments.

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Hochster So that kind of brings me to the issue of, we are giving all these things, chemotherapy, radiation therapy, surgery in one order or the other, and we call that multidisciplinary planning. How does that work and why is that important?

Johung I think that this is a long treatment course for patients. They require radiation with chemotherapy as we talked about, surgery, and then additional chemotherapy. We need to decide as a team if this patient needs radiation because then we would like to implement that radiation prior to surgery for the reasons that have talked about, so for us, typically that means that as a team of surgical oncologists or colorectal surgeons, medical oncologists as radiation oncologists together with our pathology and radiology colleagues, will meet and review cases, so that we are all on the same page in terms of the treatment paradigm which helps to coordinate all of these treatments better for the patient.

Hochster We actually talk to each other. And I do think it is really critical for most people with rectal cancer to be in a center that deals with a lot of rectal cancer and has good multidisciplinary programs where the approaches are really based on agreement of all the different specialties together.

Johung Absolutely, agree.

Hochster So, what are we doing? What is happening today with clinical trials for rectal cancer around the country and at Yale?

Johung The clinical trial we have open that incorporates radiation right now for rectal cancer at Yale Cancer Center is one that is evaluating the efficacy basically of herbal supplement which has been shown, when paired with chemotherapy, to reduce some of these GI toxicities that we have spent a while talking about and we know from animal studies for example that if you radiate mice and do that in the presence of this herbal supplements that it allows for protection of the bowel so that there is less damage seen to the bowel wall as a result of radiation, so what we are doing with this trial is basically adding that supplement to standard radiation and chemotherapy that we would give prior to surgery with the hopes that we can reduce the risk of any toxicities.

Hochster And that is traditional Chinese medicine, but in a more standardized and pharmaceutical preparation.

Johung That is standardized, and I think in general, we were mentioning other studies outside of our own institution, and I think an area that is an evolving area of interest for rectal cancer is the question of can we manage some of these patients without surgery, so

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there is a current trial that is basically looking at giving all of your chemotherapy and your radiation with chemotherapy prior to surgery and for patients who have a very low lying rectal cancer that would require permanent colostomy bag or very advanced tumors is this advantageous, perhaps could those patients avoid that surgery that requires you know a permanent colostomy. Obviously, that is something that is still an area of research and we do not know if that is the right way to go but could be promising you know evolution in the future.

Hochster Right, and also I think there are some studies coming along in the next year or so where we will be adding some of the new more targeted molecular base therapies to some of the traditional chemoradiation.

Johung Exactly.

Hochster Improve the outcome for people who are at the highest risk for recurrence of rectal cancer, the high stage III, so I mean those are pretty interesting and we are working together bringing those latest therapies to our patients here. What other advances in radiation oncology or therapy for GI cancers are we using today to help treat patients.

Johung One technique that we have not discussed yet is something called stereotactic radiation or stereotactic body radiotherapy. What this really is, is similar to that five-treatment course we were talking about prior to surgery where radiation is given in much larger doses, so the benefit of that is that if you are able to focus high ablative dose of radiation at a tumor and we can really only do this for small tumors that the ability to control that tumor is probably higher. This technique was originally used to treat cancers that are spread to the brain, so we have small brain metastases that can be basically controlled with high doses of radiation delivered often times as a single treatment. From there, that technology moved to treating small lung cancers where we have great evidence to show that it is probably equivalent to surgical treatment of those tumors where this applies to colorectal cancer is a little different, we could not use this technology to treat colon cancer or rectal cancer because those tumors are too large to be treated with this high dose of radiation, the reason being that we really rely on being very precise and focused with our treatment to a small area to avoid toxicity to nearby structures, but we know and we have known for a long time, that colon cancers or rectal cancers that spread to the liver can still be treated with curative intent meaning that if a surgeon can take out those liver metastases, those patients can have long-term survival. Often times, we have patients who are not candidates for surgery for medical reasons or perhaps the tumor is in an area, you know, that would be prohibitive to surgery or other ablative techniques that we have and so that is where

this technology of stereotactic radiation can be beneficial and we know that if we apply 3 to 5 treatments that we have a good chance of eradicating that disease that may have escaped to the liver.

Hochster So as opposed to the pre-op setting where you are giving little doses for 28 times or so, this is going to be like 1 or several big whacks at the tumor right?

Johung Exactly, you are basically giving sometimes 5 to 10 times more radiation in one dose, but in 3 to 5 treatments.

Hochster And you know in the brain the reason that this technique started is it makes it stand still or keep it from moving by putting a frame around it. You know, the liver and lungs are moving, especially the lungs when you are breathing, so what do they do for that? They cannot make people stop breathing right?

Johung For a small amount of time you could stop breathing, I am joking, but what we do is we apply what we call, there are many ways to manage respiratory motion, which is what you are getting at, so some of these technologies involve actually compressing the abdominal musculature, so that the patients are forced to breathe more shallow that limits the motion of these tumors in the liver for example. We actually obtain what we call a 4-dimensional CAT scan for planning, which you can really think of as a movie, you are getting a movie of how the liver moves as you breathe, you know, if you do not know where that small tumor is moving, you have to treat a larger area to make sure you encapsulate it, but with these CAT scans we are able to treat just the small path that that tumor would take as you breathe.

Hochster So it is really like you are hitting a moving target.

Johung Exactly and even the newer technology now involves placing these beacon transponders directly in the tumors. We used to do this actually in the prostate but now there are smaller beacons that can be placed you know into the liver would like a biopsy but instead of the biopsy taking out a specimen of tumor, you are leaving a small millimeter sized transponder in the liver tumor that communicates with our treatment machine, so the machine can basically track that tumor as you are breathing, how does it move during your breathing cycle and we can set parameters on the machine, so that if it moves 3 mm out of range, we stop treatment and wait for it to move back into the field.

Dr. Kimberly Johung is Assistant Professor of Therapeutic Radiology and Director of the Gastrointestinal Radiotherapy Program at Yale School of Medicine. If we 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 to fight against cancer here on WNPR, Connecticut's Public Media Source for news and ideas.