Dr. Linda Yin:

Hi everyone, welcome back to another episode of ENT in a Nutshell. My name is Linda Yin and I am joined today by Dr. Michelle Neben Wittich who is a Radiation Oncologist who specializes in head and neck cancers. Dr. Neben Wittich, thank you so much for being here.

Dr. Neben Wittich:

Thank you for having me.

Dr. Linda Yin:

We're going to talk about Principles of Radiotherapy today. So obviously, most ENTs are not physicists and we can't be expected to understand all the nuances, but I think it's important to at least understand some basic principles, as we will be participating in multidisciplinary management of head and neck cancers. So usually the format that we have for diseases is to talk about presentation and pathophysiology.

But we're going to shift it up a little bit this episode because this is talking about an overall treatment instead of a disease. All right, so let's start with some basic physics. So tell us how does radiation therapy work? Can you give us a simple version of this?

Dr. Neben Wittich:

So radiation therapy uses ionizing radiation to treat cancers. Ionizing radiation is radiation that is capable of ejecting electrons from an atom. Some examples of ionizing radiation are X-rays and gamma rays which are the same kind of radiation just with a different origin. Electrons, protons, neutrons, which are all particles and any other particles that contain a high amount of energy.

This energy is delivered to a patient through either a linear accelerator in the case of X-rays, or electrons, a radiation source in the case of gamma rays, or something like a cyclotron or synchrotron in the case of other charged particles, such as protons. When these particles come into contact with biological materials, specifically with DNA, it can lead to direct or indirect ionization of the biologic material which creates damage.

Direct ionization is a direct hit to the DNA molecule by the radiation, it disrupts the chemical bonds in the DNA. This is the kind of interaction that you would see with charged particles. For instance, indirect ionization occurs when the radiation gives up its energy to produce fast-moving charged particles.

This is the kind of ionization you would see with photons, or neutrons for instance. The way that the DNA actually gets damaged also occurs in two different ways. There are direct effects to the DNA and indirect effects to the DNA.

Direct action or direct effects is when the radiation directly disrupts the DNA. Indirect action or indirect effects are when the radiation interacts with something else, usually water to form free radicals. The indirect action is about two-thirds of the DNA damage that occurs in standard photon treatments.

The direct action is more common with particle treatments such as protons in head and neck squamous cell carcinoma, we most commonly use photons and protons to treat these cancers.

Dr. Linda Yin:

Great and I should clarify for the listener, we are going to be focusing mostly on the treatment of mucosal squamous cell carcinomas in this talk. Let's define some terminology. What is a Gray of radiation and what does this mean?

Dr. Neben Wittich:

Gray is a unit of measurement of the energy absorbed with radiation. It corresponds to one joule of energy per kilogram of material. They used to be called Rads, and 1 Gray equals 100 Rads. This allows us to measure the cumulative absorption of ionizing radiation that a patient receives. A larger dose of radiation for instance is required for different histologies of tumors and different sizes and amounts of tumors.

Dr. Linda Yin:

Let's talk a little bit about the biology here. So how does this ionizing radiation kill cancer cells? What is going on inside the cell?

Dr. Neben Wittich:

So that's a good question and subject of a great amount of research. Nobody knows 100% and I think there are actually many different mechanisms. Primarily what we see in studies is that radiation causes damage to DNA, and that could include single-strand breaks, DNA crosslinks, double-strand breaks and formations of various types of abnormal DNA.

Any of these things can lead to cell death and there are two primary ways that we think this happens. One is double-stranded breaks in particular can accumulate in cells. And once the cell gets enough of these, we think usually around 40, the cancer cells will not be able to multiply and go through their normal mitosis.

When they go through the mitosis and the DNA is exposed, then the cell will die as soon as it attempts to replicate and divide. Double-stranded DNA breaks can also signal the cell to die via apoptosis, or programmed cell death.

The other thing that's important about the way that radiation kills cancer cells is that it is a probability model. So radiation kills the tumor cells randomly. So each cell has the same chance of having the damage and undergoing the cell death.

So radiation kills a percentage of cells with each dose given. The other important thing, especially when thinking about cells in mitotic death are cells that are dividing quickly and replicating quickly tend to be more susceptible often to the damage by radiation because they are undergoing mitosis more frequently.

Dr. Linda Yin:

Great. That sort of brings me into my next question. So I remember talking about in medical school that radiation can kill cancer cells preferentially over the good normal cells. How does this part work?

Dr. Neben Wittich:

So that's a very good question too and a lot of patients ask how we manage to kill the cancer cells and not harm or kill the normal cells. So radiation does not have the ability to distinguish between cancer cells, or normal cells, but there are some tissue characteristics that we exploit when we use radiation both in the normal tissues and the cancer cells that can help us to have a differential in the damage that we give.

Essentially, the first way that we try to preferentially kill cancer cells is with our radiation planning. We outline all the areas where we have cancer cells, as well as all the normal tissues that we want to avoid and we design our radiation so that the high dose goes to the cancer cells, and we try to avoid dose to the other normal tissues.

However, cancer cells tend to occur in and amongst normal tissue cells. So this in and of itself is not enough to spare normal tissues. So ultimately, they do see the effects from the radiation therapy. On a biologic level, the reason that there are different effects on normal tissues and cancer cells are multiple.

The main reasons that we look at are that tumors are dividing at a faster rate, and are therefore more susceptible to DNA damage than healthy tissue. That's because of what we discussed earlier regarding the cell death that occurs during mitosis.

Most normal tissues are not growing and dividing rapidly, and so do not have that kind of susceptibility. Some of our normal tissues do divide and grow rapidly, and those would include things like skin cells, and the mucosal cells of the head and neck and those tissues do have a very similar amount of damage as we see for the cancer cells, but those are tissues that can weather this damage.

The second aspect of the differential damage to cancer cells and normal tissue is the concept of sublethal injury. Sublethal injury is injury from ionizing radiation that is not enough to cause cell death. Healthy cells by definition can repair sublethal injury, they do it constantly all the time.

We are constantly bombarded by both photons and protons in the normal environment, and our cells are able to recover from this damage because of the cancer cells rapid division. And also because usually, they have undergone a mutation that renders them unable or less able to finish damage and put checks on themselves. Tumor cells are much less likely to repair sublethal damage than healthy tissues.

Dr. Linda Yin:

Let's talk about the concept of radiosensitivity. This is a term that's used very frequently. But what is it that makes a tumor radiosensitive or not?

Dr. Neben Wittich:

The term radiosensitivity is really based on our observation of whether the tumor responds or doesn't respond to radiation, and many factors will determine whether a tumor is likely to be radiosensitive, or radioresistant. Tumor pathology plays a very important role.

Squamous cell carcinomas tend to be very radiosensitive while other tumors that occur in the head and neck such as melanomas, and salivary cancers tend to be very radioresistant. Part of this is due to the underlying pathology of the tumor and part is due to the rates of growth of the cancer cells.

Even tumors that tend to be radioresistant such as melanoma, and salivary gland cancers can be treated with radiation effectively. But often the dose required to treat them is too high for the normal surrounding tissues to tolerate.

Other very important factors in tumor's radioresistance or radiosensitivity are the size of the tumor and the oxygenation. The size of the tumor is important because as we discussed earlier, radiation kills a percentage of cells with each dose. We call it a log kill.

So one log of cells is killed with each dose of radiation. In order for the cancer to never come back, we have to go down essentially to zero and then beyond zero as far as the amount of cells that we killed which is why we use fractionation and why we use multiple doses.

Tumor sizes that are very large simply have more cells that makes it that we have to kill more cells with radiation. And that can lead to either requiring higher doses, doses beyond the tolerance of tissue, or having an incomplete response if we are not able to get enough dose in.

Hypoxia is another characteristic of many radioresistant tumors. This one is quite important and is the subject of a lot of research as far as enhancing treatment. Tumors need oxygen to be radio sensitive. The primary reason for this is that oxygen essentially makes free radical damage permanent by forming organic peroxide.

Cells on the periphery of tumors are more susceptible to radiation because they are more well oxygenated. Often, cells in the center of tumors are hypoxic, or necrotic. Because of this, ulcerative or necrotic, tumors can be more resistant to radiation.

Therefore, hypoxic tumors for any reason are much harder to treat effectively with X-rays. Anything that would increase hypoxia would decrease the effectiveness of radiation. That would include active smoking, being in a post-operative state, having prior radiation, and anything else that would decrease the oxygenation of the tumors.

Other things that contribute to tumors being more radiosensitive or resistant are as I mentioned, the rapidly proliferating tumors can be more radiosensitive, but also tumors in certain phases of the cell cycle can be more radiosensitive. That is one reason that we fractionate radiation because we can hit tumors as they go into different stages of the cell cycle by giving radiation doses at different times.

Even though many things can make tumors radiosensitive or resistant, there are ways that we can overcome this. So certain types of radiation for instance can overcome the effect of hypoxia. I mentioned that X-rays need oxygen because primarily they exert their damage through free radicals.

Neutrons need oxygen less than X-rays and they are therefore used often to treat things like salivary cancers. Large particles like carbon, which is something that is being looked into across the world are essentially independent of the presence or absence of oxygen because they do not use free radicals in their mechanism of cell killing.

Dr. Linda Yin:

Okay, now that we have some understanding of these basic principles, let's talk a little bit about more real clinical applications. So, when you see a patient in clinic for consideration of radiotherapy, what is the typical setting and what does that patient look like?

Dr. Neben Wittich:

So patients present to us both in the primary, the adjuvant, and recurrent or salvage settings. In most cases, when we use radiation, we give it as a part of multimodality treatment for head and neck cancer. We have tried to use radiation in different ways including radiation alone, chemotherapy, followed sequentially by radiation, and chemotherapy combined with radiation.

For the most part, the studies that have used chemotherapy have found that chemotherapy combined with radiation is more effective than chemotherapy followed by radiation. Chemotherapy combined with radiation is also more effective than radiation alone in most cases.

Some exceptions are early glottic cancer, early nasopharyngeal cancer and early oropharyngeal cancer which we can treat with radiotherapy alone. However, most patients in the primary setting will receive primary chemotherapy and radiotherapy together.

The chemotherapy that we use along with radiotherapy is Cisplatin, this is used as a radiosensitizer. And like some of the things that I talked about in the setting of radioresistance and hypoxia, Cisplatin can add to the effectiveness of radiation by contributing its own method of DNA damage.

The standard of care in oropharynx, nasopharynx, advanced larynx cancer and other head and neck cancers in the primary setting is chemotherapy and radiation together. The other way that we use radiation in head and neck squamous cell carcinomas is as an adjuvant to surgery.

The reason that this can often be an ideal choice for patients is that the dose that we use to treat microscopic disease is lower than the dose that we use to treat macroscopic or gross disease for reasons that we talked about earlier as far as the number of cells that we need to kill. When we use adjuvant radiotherapy, or sometimes chemoradiotherapy, this is based on the pathology findings at surgery of higher risk disease.

Another way that we can use radiation in the setting of head and neck squamous cell carcinoma is as a salvage therapy either in the setting of prior surgery or of prior radiation. After surgery or after prior radiation, the tissues are already hypoxic and this can be somewhat difficult to overcome, often needing higher doses or other intensification of treatment.

Surgical salvage after radiotherapy can often be more easily done although I know it's not that easy to operate on radiated tissue. The other ways that radiation can be used are occasionally as a neoadjuvant treatment prior to surgery.

This is not a common approach, but in some cases such as sarcomas, or such as cases where we are trying to spare something like the eye, we will use neoadjuvant radiotherapy to decrease the size or involvement of a tumor and try to achieve a better surgery in that way. The last way that we can use radiotherapy is for palliation.

This can be used to decrease pain or other symptoms caused by the cancer and can be given in many different ways either sometimes with or usually without chemotherapy.

Dr. Linda Yin:

When you see a patient in clinic and you're considering using radiotherapy, what sort of important things do you focus on when you take their medical history?

Dr. Neben Wittich:

So whenever we see a patient that presents with a head and neck cancer, we will discuss with them what their current function is, their functional status in general, their general health, their smoking status, the presence of other diseases such as connective tissue diseases, or syndromes that can predispose to radiation sensitivity, and things like kidney disease or immunosuppression. We also assess the swallowing function, their airway status, either because a tumor is involving or compressing the airway as a risk for possible swelling because of mucosal edema.

We also look at their nutritional status. And I also ask about history of prior radiation treatment, particularly any treatment that would be in the same region.

Dr. Linda Yin:

What about physical exam? What sort of physical exam is important specific to radiotherapy?

Dr. Neben Wittich:

So we would examine and palpate the tumor, as well as the neck for lymphadenopathy, looking for fixed nodes, looking for bilateral nodal disease. I would examine cranial nerves, particularly for tumors in the high oropharynx or nasopharynx and we also look carefully at their dental health, as this is something we can impact and also prevent during your course of radiotherapy.

Dr. Linda Yin:

Let's talk a little bit about workup prior to starting radiation treatment. What kind of imaging workup is necessary before starting radiotherapy?

Dr. Neben Wittich:

Generally, we will obtain a PET/CT which is most helpful for us because it shows us both anatomic as well as functional aspects of the tumor. We will often also get a CT of the neck with contrast either as a part of our planning or prior to planning and sometimes a CT of the chest if needed to look for metastatic disease.

We also obtain a dental referral and Panorex to look for non-restorable teeth, or any evidence of dental caries or poor dental health. In addition, we will perform swallow evaluation and have them see speech and swallow therapy, as well as get involvement of our dietitians early on and our physical therapists early on as well to work on range of motion and lymphedema.

Dr. Linda Yin:

I understand that in treatment of head and neck squamous cell cancers in particular, it's important to work in a multidisciplinary team. What are some important points that you focus on or discuss with the surgical team and medical oncology team before you formulate a good radiation treatment plan?

Dr. Neben Wittich:

I think as in many sites, tumor boards are very important. I think they are particularly important in the head and neck site as there are many subtle things that can be discussed between the groups that can make quite a large impact on the treatment.

In our tumor board, the decision on the best therapy that we recommend is based on input from medical oncologist, ENT surgeons, radiation oncologist, but also our swallow specialists, our dietitians, our dentists and other groups that get involved with these patients care. In particular, from my standpoint, prior to any intervention, if radiation is going to be the sole modality or chemoradiation, it's extremely helpful to discuss with our radiologists as well as with our surgeons the extent of the tumor, the size, the location, and any involved organs.

After surgery, it's critical to be able to communicate with our surgeons to the extent of the resection, the reconstruction, anything encountered at surgery as particular areas of concern. This is quite important for our treatment planning.

Dr. Linda Yin:

I understand that a simulation is done prior to initiation of treatment. What is a simulation? And how can this help you with planning?

Dr. Neben Wittich:

A simulation is essentially a planning session to be able to design and deliver radiation. The first thing that we do is get the patient in a position that we think is going to be reproducible on a daily basis for several weeks.

In order to do that, we have a thermoplastic mask that goes over the face and shoulders and this is indexed to our treatment table and our treatment system. This is made to keep the patient in the same position every day. We will often use something like a Bite Block or other oral devices as well to be able to position things like the tongue, the mouth, the palate in a way that helps us to deliver our radiation.

When we get the patient in this position, we obtain a CT scan and use that CT scan to outline every area that we want to treat as well as all the normal structures that are in the head and neck that we want to avoid. When we do that scan, we make a mark on the patient with a permanent tattoo that represents what we call our isocenter which is the area around which our beams rotate, essentially our focal point.

Dr. Linda Yin:

Can you talk a little bit about how you're using that CT scan for treatment planning and what exactly you're outlining and how you're doing that?

Dr. Neben Wittich:

So we use the CT scan as well as sometimes MRIs, the pretreatment pet and pretreatment CT and the discussions with our surgeons and radiologists to be able to outline our target. The target is based on the tumor location, the surgery and the tumor behavior and its potential paths of spread.

The goal of treatment planning is to choose the most appropriate beams to be able to reach the target, but also minimize damage to the surrounding healthy tissues. In the head and neck, there is a lot of both target and healthy tissues and they mostly occupy the same space.

So complex anatomy as well as different shapes and geometry all need to be considered and the treatment planning of head and neck cancers is very complex. Initially, we would use treatment planning that was called two-dimensional radiotherapy where we would essentially have a beam coming from the right side and the left side and we would outline on a radiograph the areas that we wanted to treat.

This would of course treat everything from the skin to the subcutaneous tissues, all of the mucosa and then skin subcutaneous tissues on the other side. Subsequently, three-dimensional conformal radiotherapy was developed. What this was able to do was use CT planning in order to deliver radiation therapy.

Even in that setting, there would be fixed beams coming from different angles and while you would be able to modulate some of the dose and create some shapes, it was still somewhat difficult to treat things that were oddly shaped or mixed in with normal structures. Most recently, Intensity Modulated Radiation Therapy or IMRT has been developed.

This delivers radiation in a different way where you have a large beam that's broken into multiple tiny beamlets. Those beamlets deliver different intensities of radiation across the field depending on how much radiation we want to go, how much we want to protect something and what is in the area.

With this, we can essentially treat things that are any shape, any size, and spare things that are outside the field, or even right next to the field. We use dosimetrists which are highly trained specialists who are able to use computer algorithms to help create dosimetric maps, using something called inverse planning.

They give us ideal plans based on the number field, size of the fields and then the modulation. This is able to give us the topographic map that we see when we look at radiation plans which show us which structures receive how much dose.

We also work very closely with medical physicists who are able to go through and make sure that what the computer is saying is the same thing that's actually happening in the patient based on our machines, delivering what they say they are, as well as the planning system being accurate. The way that they do those is they actually put what we call phantoms on the table.

They radiate them, and they use dosimeters to measure what radiation is going to different parts of the human analog to make sure that what we've planned is what we are delivering.

Dr. Linda Yin:

I think this is a good segue now and talking about actual treatment options. So one thing that's always confusing for resonance I think is what the difference is between external beam radiation. So EBRT and intensity modulated radiation therapy, as you mentioned IMRT. What is the difference between those terms?

Dr. Neben Wittich:

So external beam radiation therapy is an umbrella term that delivers any kind of radiation therapy delivered from an external source. The contrast here is to something called Brachytherapy where a radioactive source is actually placed in the patient, either via needles, an applicator, or in other ways and delivered directly to those tissues.

IMRT is a kind of external beam radiation, 3D conformal radiotherapy, as well as 2D radiotherapy are also kinds of external beam radiation. Gamma Knife radiotherapy would also be a kind of external radiation. Proton radiotherapy would also be considered external beam radiation.

Dr. Linda Yin:

Let's talk now about some specifics of dosing regimens that are used in the treatment of head and neck cancer. How many grades are usually given in what settings?

Dr. Neben Wittich:

In the setting of primary chemo radiation therapy which is the most commonly delivered primary radiation treatment, we deliver 70 Gray. This is broken up into 35 treatments of 2 Gray each delivered Monday through Friday. This is given with concurrent chemotherapy.

In the setting of adjuvant radiotherapy that we give due to multiple factors such as locally advanced disease, multiple lymph nodes involved, the dose that we give is dependent then on the pathology found at the time of surgery. The dose range from 60 to 66 Gray depending if we are treating microscopic disease, positive margins or potentially even gross disease, the clinically negative neck gets 50 to 54 Gray.

The reason for our ability to deliver this lower dose to what we are considering microscopic disease in the clinically negative neck versus microscopic disease in the post operative neck is that hypoxia that we talked about before. When there's no hypoxia, 54 Gray is sufficient.

We will also sometimes add chemotherapy primarily for positive margins or extracapsular extension found at the time of surgery. When we deliver adjuvant radiotherapy, one of the most important things that we look at is the timing.

We need to require adequate healing from the surgical resection of at least two to four weeks, but our optimal radiation timing is within six weeks of surgery. The timing is critical to get the maximum benefit of the radiation. Essentially, what we are looking at is called a treatment package time which is from the day of surgery to the last day of radiation being less than approximately 11 or 12 weeks.

This is because of accelerated repopulation that can occur in squamous cell cancers several weeks after any treatment is started. We know that if we prolong the treatment package time, we lose both local control and overall survival.

So it's always a balance between healing and being within the six week window to get the maximum benefit out of our treatment. We will sometimes as I mentioned earlier also use preoperative radiotherapy either for debulking tumors, or in the case of sarcomas.

Typically, this dose would be lower approximately 45 to 50 Gray. The reason that we would ever use preoperative treatment is either to try to debulk a tumor, or in cases where we can use a lower dose and a lower volume of radiation than we could if it was postoperative in the setting of critical structures.

Dr. Linda Yin:

Okay, let's talk about another important concept now that we've already touched upon. What is fractionation?

Dr. Neben Wittich:

So fractionation refers to delivering smaller doses of radiation with each treatment spread over time rather than one large sum dose. This is a question I get a lot from patients when they ask me why they have to come live with me for six or seven weeks, and why I can't just give them all the dose at once.

We could give all the dose at once, and it would definitely be the end of the tumor. It would be highly effective treatment, but the problem is the tumor living within all of our normal tissues that we are trying to spare when we're doing organ preservation.

So we have to give the radiation in a way that kills the tumor, but doesn't kill or at least permanently damage our normal tissues in the area. So there are several other rationales for fractionating treatment. One is that we talked about a little before where cells are more susceptible to radiation in certain portions of the cell cycle.

For instance, when they are dividing, when they're trying to grow and in mitosis. So when radiation is fractionated, you have 30 or 35 chances to catch any certain cell in the most sensitive part of the cell cycle.

Fractionation also gives our normal tissues greater time to repair which should give them the advantage that I was talking about over the tumor cells that are less capable of repair. And lastly, fractionation gives hypoxic cells time to recover and reoxygenate which can make them more susceptible to future fractions of radiation therapy.

Dr. Linda Yin:

There are a lot of terms thrown around regarding fractionation, hypofractionation, hypo-accelerated, can you help define some of these for us and explain the differences?

Dr. Neben Wittich:

Conventional fractionation is one treatment per day, five days per week, that was what I was talking about in the previous section of primary chemoradiation and adjuvant treatment. There are actually quite a few different ways to fractionate the radiation depending on what you're trying to achieve.

One of the ways is hyperfractionation. Hyperfractionation is giving more than one treatment per day. Generally speaking, this is two treatments a day with a smaller dose with each fraction, but the same overall duration of treatment. We're usually able to get to a higher overall dose with this method and it is felt to decrease late toxicity.

In particular to certain tissues such as nervous system tissues. You can take hyperfractionation a step further, something called accelerated hyperfractionation. In that setting, you give radiation twice a day, you often will use the same overall dose, but decrease the total time of radiation.

This also feels like it can give potentially a better response rate than conventional fractionation primarily in some ways because of the treatment package time or the total time being shortened. There is also something called a concomitant boost accelerated fractionation.

Essentially, what that is, is you do your normal length of radiation with once a day treatment at the beginning, but often over the last two weeks in the afternoon, you give an extra dose of radiotherapy. So you end up with twice a day for part of the treatment.

Lastly, there are hypofractionated regimens. Hypofractionated regimens is giving a higher dose, but less fractions of radiation and also usually, a less total dose of radiation. This allows us to shorten the total treatment time, that treatment package time, but get in the same effectiveness of dose.

Hypofractionation can be most useful in tumors such as melanoma, salivary tumors, those tumors where we are trying to overcome an inherent radioresistance or a radioresistance due to hypoxia. The reason that this helps us to overcome radioresistance is giving larger single fraction doses can often overcome a lot of the cell's ability to repair their damage.

One last way of modifying a fractionation is to deliver six treatments per week instead of five. In that way, we would give for instance, 35 fractions, but we would do it in six weeks rather than seven. And the way we would do that is giving a double treatment once per week.

The goal of that is also to shorten that treatment package time. Many of the modified fractionation regimens are designed to increase the effectiveness of radiotherapy. For instance, many of these different fractionations are used in a setting where we are trying to do primary or adjuvant treatment, but we cannot use chemotherapy.

The different fractionation is designed to give that extra effectiveness we would normally get from the chemotherapy. It's also used as I mentioned in settings where we're trying to overcome either hypoxia or radioresistance. The last setting that I would use in altered fractionation would be if we do get out farther than the six weeks for an adjuvant treatment. I may do six fractions per day, and shorten my course to five weeks to make the treatment package time still be in the appropriate range.

Dr. Linda Yin:

Can you talk a little bit about the shrinking field technique? I've heard about this in the setting of particularly laryngeal tumors. What is it?

Dr. Neben Wittich:

So a shrinking field technique is essentially to treat a large area of clinically involved disease and potential regional lymph nodes to an initial dose, and then over time, reduce the field size, essentially to

give boosts of radiation to only the areas of gross tumor with a smaller margin. This technique was more common in the days that we did three-dimensional radiotherapy.

In the setting of intensity modulated radiotherapy, IMRT, we often don't use this technique anymore, because we can give different levels of dose at the same time to different areas. That's called a simultaneous integrated boost.

Dr. Linda Yin:

Can you explain a little to us some of the differences between the different particles? Every patient wants to know about proton therapy. What's the difference between protons, photons and even neutrons?

Dr. Neben Wittich:

Yes, that's a very common question that we get these days. Different particles, different types of radiation can have very different properties and behaviors when used for radiation therapy for cancer. X-rays for instance have an entrance dose and an exit dose and primarily give their dose at a certain depth in a patient.

For X-rays, if we want to give dose to an area, let's say in the center of a patient, we give it from multiple angles so that at that, what we call isocenter or the place where we want our dose to be our high doses given, but there's low dose that goes essentially all around the patient from all the entrance and exit of the other beams.

Protons, on the other hand are unique. They are both heavier than photons and they also have a very different behavior when used to treat cancer. They have something that is called a Bragg peak which is a sharp distal dose fall off. Additionally, they deposit very little dose at the entrance.

What this allows is for us to target something in the center of a patient without having significant dose accumulating at the entrance and not having any dose falling off. Theoretically, this allows delivery of high doses of radiation to a tumor, but without the low-dose spread that we get with other techniques even such as IMRT.

In reality, this is certainly possible and we have seen it in many tumors, particularly central nervous system tumors, but in the head and neck, tumors form complex 3D shapes, tumor anatomy changes with treatment, particularly in the primary setting. Patients lose weight or have different setups and so protons can and are very frequently used in head and neck cancer, but it takes very precise planning.

It takes frequent verifications, it often takes replanning as tissues change through treatment. These things can optimize the benefit of proton therapy, but makes it more complicated, time intensive and difficult to deliver.

Neutrons are heavy neutral particles that can result in a greater direct injury. They're not as dependent on the cell cycle and proliferation. They're not as dependent on oxygen, and they can be used most commonly to treat salivary cancers. They are not offered in a significant numbers of places in the United States, but there have been many studies showing their benefit in salivary cancers.

Dr. Linda Yin:

Let's talk now a little bit about something that we frequently blame you guys on which are toxicities of radiotherapy. So what are some of the acute and late toxicities that you can see?

Dr. Neben Wittich:

Yes, this is definitely something that's very, very major in our field, not just acute toxicities and getting people through treatment, but what we know can happen long-term and permanently. So when I talk to patients about their radiation toxicities, I would break them down into acute and late toxicities.

They have different mechanisms. So the acute toxicities are based on inflammation essentially. So you will get skin changes, radiation dermatitis which can go from redness to essentially a blistering sunburn.

You get the same thing that happens in the throat, a mucositis that can go from dry and red to essentially ulcerations. You will also get changes in things like glandular tissues, including xerostomia from salivary glands which are very sensitive, taste changes from the taste buds which are very sensitive, alopecia in the ... From changes to the hair follicle.

You will also get other things related to inflammation such as thick mucus which is basically what small amount of saliva they're trying to make and in the setting of extreme dryness and significant inflammation, this can be very bothersome for people. People also will notice hoarseness, often from the dryness, but also from edema.

People will have edema in the mucosal surfaces, edema in the larynx. The edema also can cause ear plugging, that will happen during treatment in many cases. People also will get generally fatigue, nausea. They can have difficulty eating and drinking because of all of these things and require PEG tube placement.

We'll sometimes have to use IV fluids to keep them hydrated. We generally try to keep them out of the hospital. All of these acute effects don't happen right away. Primarily in the first two weeks, people are dry because of the changes in the salivary glands and they often have some taste changes, they have a bit of dry skin.

But it's approximately the third or fourth week of radiation as those daily doses accumulate where people start to have more of the obvious inflammation in the skin on the inside of the throat. Essentially, you don't get the two first weeks for free.

At the end of radiation, they essentially have two weeks after treatment is done where they can have either worsening or at least continuation of their maximum side effects. The acute toxicities are expected to almost all resolve and that can take about four to six weeks for the inflammatory changes to resolve.

Meaning, the skin changes and the mucositis. Some of the other changes like the glandular changes can take longer, or can become more late effects. So I'll talk about generally the late effects now.

Late effects unlike acute effects are not due to inflammation, but they're due to the consequences of both the inflammation and the repair. They're also due to decreased in circulation and scarring essentially, fibrosis.

The most common late effects are xerostomia which will persist in most patients to some extent even though it does improve very significantly. This can lead to problems with dental caries. This can lead to issues with having to have teeth extracted and can result sometimes in osteoradionecrosis if they have to have an extraction in the setting of radiation.

Osteoradionecrosis can also happen de novo, but that's much more unusual. Osteoradionecrosis in general with good dental care is approximately 2% of people that have undergone radiation. Xerostomia itself is extremely common and I would say the majority of people will have that.

We use fluoride treatments and dental visits to try to prevent the negative effects of this. Muscle fibrosis is the other thing that I would say many, if not all patients will eventually get. This leads to neck stiffness, decreased range of motion, and can be painful for patients as well.

We have them see a physical therapist to go through stretching, and other things that they can do to really prevent this. It's much easier to prevent it than to treat it. Treatment though can include things like Vitamin E and Pentoxifylline, intensive physical therapy, and other interventions.

They can also get skin fibrosis or pigment changes. These don't tend to be as bothersome as the muscle fibrosis, but can also be bothersome to people. Taste changes generally will improve to close to 100%, but there are almost always things that just don't taste the same.

Lymphedema is something that is also common. It's also essentially due to circulation issues, circulation through the lymph. This is something that we also have people see physical therapist for. This can be very bothersome for people if it becomes chronic, but is something that can be prevented with intensive physical therapy.

People can also have swallow changes both because of pharyngeal constrictor dysfunction, laryngeal excursion or other laryngeal dysfunction, and esophageal webs or strictures. Many of these things can be improved with speech therapy, swallow therapy and or use of dilations for the esophageal strictures. And these are all essentially also fibrotic type of changes.

People can have hypothyroidism develop as well, this is quite common. More than 50% of patients will eventually have decreased thyroid function. We check the TSH every six months and people who have had radiotherapy in order to be able to treat thyroid dysfunction before it were to manifest clinically.

People can also have persistent Eustachian tube dysfunction, ear plugging, otitis media and sometimes have to have myringotomy tubes placed because of it. Those are mainly things that are due to issues with scarring and circulatory problems.

People can also have circulation issues develop over time in the carotid artery, leading to carotid atherosclerosis. This is something that would happen more commonly in someone who has other risk factors, but can happen in people with very few risk factors.

We will tend to do carotid ultrasounds to screen for any atherosclerosis and also treat with risk management in patients who have had radiation to the neck. Some other potential, either complications or side effects that are rare that can be catastrophic would include damage to the larynx, depending if the larynx is the target or just in the area that can be up to 2 to 5% for larynx as a target, much, much less in the adjuvant setting where we're not treating the larynx.

Other potential late complications that are very rare, but catastrophic can include carotid blowout. Generally, this is most common in the setting of either an extensive surgery or prior radiation or both. Lastly, radiation, even though it's used to treat cancers can also cause cancers.

There is a possibility of developing a second cancer due to radiation. This is quite unusual in adults. The risk is approximately one in 10,000 per year, and often would occur in the medium or low doses of the radiation field. These could include thyroid cancers, meningiomas, skin cancers, or sarcomas.

Dr. Linda Yin:

Okay, and finally, let's talk about follow up and surveillance. When do you usually see patients back after treatment for radiotherapy?

Dr. Neben Wittich:

I would usually see people back initially six weeks after completion of radiotherapy. This visit is primarily to ensure that they are healing appropriately and getting over the acute effects of radiotherapy.

We would not do any scans at that point because they would still have significant inflammatory changes which would not be distinguishable from any potential recurrent tumor. We would generally do a PET scan and other imaging that's necessary at three months after radiotherapy.

I would then see them back every three to four months for two years and then every six months up to the five year mark. I also tend to see my patients yearly indefinitely, primarily because of the late effects that we talked about in order to continue to manage those effects and try to optimize their quality of life.

Dr. Linda Yin:

All right, so those I think are all the questions I had on radiotherapy. Anything else that we haven't talked about that you feel like is important to cover?

Dr. Neben Wittich:

No, I think we covered the main important things. Thank you.

Dr. Linda Yin:

Awesome. Thank you so much for being here. Okay, let's move on to our summary section now. So radiation therapy is the delivery of ionizing radiation consisting of a high energy particle and this particle can be a photon, a proton, a neutron, or even a carbon therapy in the future.

Radiation and flick cell death are the two major mechanisms. You can have direct damage through ionization of DNA, or you can have indirect damage through ionization of surrounding molecules like water that then produce free radicals which then go on to cause damage.

On a cellular level, radiation creates many different kinds of DNA injuries that eventually lead to cell death and this can occur most commonly during the mitotic phase of a cell cycle, or it can occur through programmed cell death or apoptosis.

Radiation kills cancer cells preferentially over healthy tissues only because of some different properties and cancer cells can divide at a faster rate that makes them more susceptible to DNA damage and also makes them less likely to repair any sublethal injuries. Radiosensitivity is a term that describes how cancer responds to radiation therapy and this can be determined by the tumor pathology by its size, and by the extent of hypoxia that's within the tumor.

In head and neck squamous cell carcinomas radiation can be delivered in several settings. It can be given in the primary setting either as a single modality treatment or concurrently with chemotherapy and in that latter scenario, 70 Grays is given. It can be given adjuvantly in the postoperative setting where typically 60 Grays are given, or in the other less common settings like palliative or preoperative debulking.

Simulation and treatment planning are crucial before initiating treatment and this involves choosing the right doses and the right paths for the beams to reach the target while also minimizing damage to the surrounding healthy tissues. In head and neck squamous cell cancers, radiation is typically delivered with an external beam.

Hence, EBRT. IMRT is a special type of EBRT that's now widely used and instead of a single beam, this uses lots and hundreds of smaller beams each with a different intensity level allowing specific

mapping of each beam so that it delivers a dosimetric map that's favorable to giving the highest doses to the tumor and lowest doses to surround the healthy tissue. Fractionation is the delivery of smaller doses of radiation, with more frequent treatments spread over time, rather than one large sum dose.

And there's several rationales for fractionating, but in general, it's felt to maximize tumor cell death and minimize the death of healthy tissues. Acute toxicities of radiotherapy typically come on about two to three weeks into treatment and can include skin irritation, mucositis that can be severe, it can also include xerostomia or dry mouth, dysgeusia, changes in taste, mucosal edema and they typically resolve by six weeks after therapy.

Late toxicities can include some of the same things like xerostomia. It can also include dental caries, osteonecrosis, dysphasia, esophageal strictures, and a rare catastrophic cases and this can occur even years after radiation therapy. It can lead to things like carotid blowout or secondary malignancies.

Let's move on to the question session. So I'm going to provide a question and give you some time to think about the answer. And then I will follow up with the answer. So what is a Gray of Radiation and what does this represent? 1 Gray of Radiation is a Joule of energy per kilogram of material and this is just a measurement of the dosage of radiation. 1 Gray is the same as 100 Rads.

Which part of the cell cycle is most susceptible to damage from radiation therapy? Cells that are undergoing mitosis where there is DNA synthesis and replication are at the greatest risk of death from radiation therapy.

What are some special circumstances in head and neck cancer where radiation can be used as a single modality treatment? Radiation can be used as a single modality treatment for early glottic cancers, nasopharyngeal cancers or oropharyngeal cancers.

What is the typical regimen for conventional fractionation? Typically, conventional fractionation means giving one treatment of radiation per day, five days a week. Hyperfractionation will be giving twice a day treatments with smaller doses per fraction, the same overall duration, but usually a higher overall dose. All right, and that's our talk. Thank you so much again for being here.