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The Use of TORS for HPV-Related Oropharynx Cancer

Moderator:

Welcome to Medical Breakthroughs from Penn Medicine, advancing medicine through precision diagnostics and novel therapies. Your host is Dr. Lee Freedman.

Dr. Lee Freedman:

Oropharyngeal cancer makes up a growing proportion of head and neck malignancies. To some extent, this has been associated with the increase in infection of the oropharynx by oncogenic strains of the Human Papillomavirus, or HPV. Transoral Robotic Surgery, or TORS has allowed for minimally invasive surgery for HPV-related and non-HPV-related oropharyngeal cancer. I am your host, Dr. Lee Freedman and with me today is Dr. Gregory Weinstein, Professor and Vice Chair and the Director of the Division of Head and Neck Surgery. He is also the Co-Director of the Center for Head and Neck Cancer in the Department of Otorhinolaryngology, Head and Neck Surgery at the University of Pennsylvania.

Dr. Weinstein, welcome to the program.

Dr. Gregory Weinstein:
Thanks very much.

Dr. Lee Freedman:
Why do we not start very basically with the question, what exactly is TORS?

Dr. Gregory Weinstein:
TORS is Transoral Robotic Surgery. Back in 2004, my colleague Bert O'Malley and I began research applying the da Vinci surgical robotic system, which is made by Intuitive Surgical, to tumors and lesions of the throat.

So what TORS is, is it allows the three arms of the robot to be put into the mouth and allows us to resect cancers or benign lesions or benign tumors that, in the past, was required a rather extensive operation to remove, or an alternate nonsurgical treatment, such as radiation or chemoradiation, which in some cases, is not as effective as surgery and so this is what transoral robotic surgery is.

Dr. Lee Freedman:
So the advantage seems to be that it's much less invasive when you compare it to a traditional surgery?

Dr. Gregory Weinstein:
Exactly and these little tools that are at the end of the robotic arms, move exactly like your hands do. So essentially, what it is, you can consider it like miniaturization of your hands and working in the mouth in tight spots that we normally would have trouble getting to
In 2009, the FDA cleared transoral robotic surgery for T1 and T2 malignancies and benign tumors of the throat and last year, the FDA cleared removal of benign tongue-based lesions.

Dr. Lee Freedman:
I would imagine this is a skill that needs to be developed. What is the process of learning this technique and how many surgeons across the country are adept at this?

Dr. Gregory Weinstein:

So back in 2009, after FDA clearance, it was necessary to do what we call postgraduate surgical training. Postgraduate surgical training means that practicing surgeons who are out there, this is new technology and the new approach, need a way to learn these techniques so that they can, if they choose to, apply them in their practices.

So we began a training program at the University of Pennsylvania, which is done in conjunction with the robotics company and what the training approach has done, is it allows surgeons to get online training on the web and then, inadamant training done in computer packages that are in the console of the robot that they do back at their home hospital. Then, they visit the University of Pennsylvania, spend about eight hours doing a pig lab where they deal with live tissues.

Then the next day, they do have a day of cadaver work with either Bert O'Malley or myself and then, they observe cases the following day in the operating room and watch what we're doing and the OR set up and how we use the instruments and how we do the cases. Then, finally, they go back proctorships for these surgeons in their first couple of cases.

So it's been an approach that has yielded, I think since 2009, over 250 trainings of individual surgeons. Prior to that, we had surgeons coming from around the world, about 50 surgeons, so about 300 surgeons have been trained at the University of Pennsylvania. We're the primary training program in the world for this technology and now, several thousand TORS cases are done annually, worldwide.

Dr. Lee Freedman:

Oh, that's fascinating, so a very broad-reaching training program involving many modalities, all based, really, out of your program at the University of Pennsylvania?

Dr. Gregory Weinstein:

That would be accurate.

Dr. Lee Freedman:

I imagine that this technique results in much lower morbidity. It's been five, six years since it's been approved, do we have efficacy measures for this versus more standard treatments?

Dr. Gregory Weinstein:

Well, to get FDA clearance, essentially what we did was, we compared the results... I'll backup for second. Back in 2006, we felt that it was important to get others doing research in transoral robotic surgery. We set up a training program, that was a research training program for 12 surgeons from around the country and this included surgeons from Mayo Clinic, University of Alabama, MD Anderson and Mt. Sinai in New York, from numerous institutions around the country and then, we gave them our research protocol, showed them how to do the surgeries that we were doing back in 2006 and then, encouraged them to do research at all these institutions began research programs.

Ultimately, we pooled the data from the University of Pennsylvania in 2009, the University of Alabama and the Mayo Clinic and with one of my colleagues, Chris Holsinger who was at MD Anderson, now is at Stanford as a Data Safety Manager.

The data from our work was given to the FDA and basically, it compared to historical findings in the literature for standard surgery and for radiation and chemoradiation and was found that on an oncologic level, it was at least equivalent, or better than many modalities and on a functional level, was again, equivalent or better.

If we look specifically oropharyngeal cancer, because oropharyngeal cancer, there has been an epidemic of HPV-related oropharyngeal cancers in the United States and this has been really the home that TORS has found. It really is an excellent treatment modality for tonsil cancer and tongue-based cancer.

If you look at that specifically, the cure rates that have been published in the literature for HPV-related cancers, are over 95 percent using transoral robotic surgery and the key issue is, functional outcomes.

In other words, can the patient still swallow and speak well and the functional outcomes have been outstanding, as well, with a very low, what we call, PEG dependency, when patients can't swallow after an aggressive treatment in their throat, they have to have a stomach tube and the PEG dependency rates have been on the order of less than one percent, or two percent and the same for tracheostomy rates, which is, in some patients, because of swelling, would need that.

Now, when you look at the alternative treatment for oropharyngeal cancer, it's high-dose chemotherapy and radiation, typically, cisplatin-based chemotherapy. New technology doesn't get developed, it doesn't get accepted, it doesn't get adopted by the community, unless the thing it's replacing has problems.

The reason we did this research, particularly on oropharyngeal cancer, was that the standard high-dose chemoradiation is way too

intense, by treatment, with significant side effects and the side effects include, a long-term risk of a permanent stomach tube of about 10 percent in the best of hands, if you look at the literature.

Then, in terms of cure rate, we, right now, when we look at this, we say that chemoradiation, that HPV-related cancer is highly curable with chemoradiation, but in fact, if you look at the existing data, if you look at the patients and it's been done, looking at ROTG patients, for instance.

If a patient is a nonsmoker, then, regardless of the stage of the HPV-related cancer, they have about a 93 percent overall survival at three years. If they have a 10-pack year smoking history and they have more than one lymph node in the neck, the cure rate drops down to 67 percent. Then, if they're not HPV-related, the cure rates from chemoradiation at three years are about 47 percent. That's disease-free survival.

Now, if you look at TORS, regardless of HPV status, or smoking status, we published this data recently in Head To Neck Journal, it's over a 95 percent cure rate regardless of whether they were smokers, or numbers of lymph nodes and so forth. So the home that TORS has found, is as an alternative to high-dose chemoradiation.

Dr. Lee Freedman:

Very impressive. If you're just tuning in, you're listening Medical Breakthroughs from Penn Medicine on ReachMD. I'm your host Dr. Lee Freedman and I'm speaking with Dr. Gregory Weinstein, Professor and Vice Chair and the Director of the Division of Head and Neck Surgery at the University of Pennsylvania.

Dr. Weinstein, let's turn to HPV, what is the connection with HPV and oropharyngeal cancer?

Dr. Gregory Weinstein:

There's a number of HPV-related viruses. The one that causes head and neck cancer tends to be HPV 16 and HPV 18, but mostly HPV 16. If you look at the CDC website, 50 million Americans have been exposed HPV virus.

Now, normally what happens with the virus, it gets integrated into the cell and takes over the DNA mechanism, reproduces itself as viral capsid, destroys the cell and then is dispersed and is infectious and moves on.

Well, with HPV and this kind of oncologic virus, in some patients, the virus gets integrated into the DNA of the cell and automatically turns itself off from replicating and then, resides there, not being infectious, because really, the infectious point appears to be about six months to a year and then, it's not longer infectious, but in some patients, it's integrated itself into the DNA and then, kind of resides there for decades and then, several decades later, anywhere from 20 to 40 years later, these cancers start to show up.

This is the same virus that causes cervical cancer, but unlike in women, we don't have a Pap Smear yet or early detection method for finding these cancers. So the way these cancers tend to be found is when the patient develops a lymph node in the neck because they tend to be silent and relatively small in the throat.

So really, the way they're showing up is by a lymph node, which automatically makes it stage 3 and stage 4, but still is very highly curable because the primary sites are mostly T1 and T2, they're perfectly amenable to transoral robotic surgery.

Dr. Lee Freedman:

And when we say de-intensification for this type of process, what does that mean?

Dr. Gregory Weinstein:

So, you know, it's very interesting, you know the Pub Med database, which has 24 million entries, it's our Google, right, doctors Google for looking up articles, if you put the word de-intensification into Pub Med, 26 articles come up, that was about a few weeks ago when I was checking before the lecture I gave, I was just curious, 20 out of the 26 articles are related to high-dose chemoradiation for oropharyngeal cancer. It boggles the mind. There are 24 million entries and the only treatment that is considered so intense that the term de-intensification pulls up almost all the articles is high-dose chemoradiation for oropharyngeal cancer.

So what our goal is, is to try and de-intensify the amount of radiation we're giving to people and less chemotherapy because high-dose radiation has to be given in a wide field when you haven't done the surgery, with high doses and has to be given in conjunction with chemotherapy, which also increases the toxicity in the throat.

Then, the delicate muscles of swallowing can be damaged so that patients can have real difficulty swallowing long-term. So when we say de-intensification, but we mean is, do the surgery, they heal, they do very well, then, we want to decrease the radiation dose for the primary site into the neck, avoid chemotherapy in about 40% of patients and then, decrease the total dosage and field size that we do at the primary site said this de-intensifies the treatment.

It doesn't have collateral damage to the swallowing muscles, so that's really important because these cancers, which by the way,

essentially are caused by normal sexual behavior, these cancers tend to occur in 40 to 60 year age group. They tend to be healthy people that are physically fit and are very health conscious, frequently have either quit smoking in the distant past, or don't smoke at all. It's a real, what happened here, I did everything right. I was eating right. I'm exercising, an otherwise healthy people.

Now, if you take that group of patients and then, you give them an incredibly intense treatment that damages their swallowing function, it really has a negative impact on quality of life and they have a lot of living to do because it's a highly curable cancer. The goal is to de-intensify. Now, there's other ways that are being looked at to de-intensify with other chemotherapy and radiation regimens, but TORS is FDA cleared, 20 percent of patients avoid radiation entirely. This is a viable method for providing the de-intensification for our patients.

Dr. Lee Freedman:

Absolutely. From what you said, the efficacy is excellent and you avoid all the morbidity of those other very intense treatments.

Dr. Gregory Weinstein:

Well, not necessarily all the morbidity because 80 percent of patients are still getting radiation, but you decrease the morbidity.

Dr. Lee Freedman:

I stand corrected, you decrease it. Absolutely. Now, as we look ahead Dr. Weinstein, what do you see for the future of TORS?

Dr. Gregory Weinstein:

Well, right now, there's a couple things going on. There's a number of trials around the world looking at even further de-intensification. There's an NCI-funded trial from ECOG, the Eastern Cooperative Oncology Group. I'm the Director of Surgical Quality on that study.

What that study is looking at is patients go through transoral surgery, primarily, transoral robotic surgery and then, if they're kind of intermediate group, they get randomized between 5,000 versus 6,000 rounds, which is an opportunity to lower the dose. Typically, when patients have extra capsular spread, or cancer spread outside the lymph node, which is discovered when we remove the lymph nodes, as part of this surgical paradigm, they typically get chemo and radiation.

In our study, National Multi Institutional Trial, we are avoiding chemotherapy in the groups that have minimal extra capsular spread. So this is a way of de-intensifying treatment. There's an in-house study at the University of Pennsylvania where we are also not radiating the primary site at all, if patients don't have any high-risk features. So they go for the surgery and if they have neck indications for radiation, which is multiple positive lymph nodes, or cancer spreading outside the node, then, they would get radiation or chemoradiation, but we would block out the primary site entirely.

We know this is safe because we published data showing that in patients who don't get radiation at all after transoral robotic surgery, the risk of recurrence at the primary site is only about two percent.

In our cohort that didn't get radiated, the cure rate is incredibly high with a two to four percent recurrence rate, we saved radiation. Remember, radiation can only be given to one body part per lifetime, generally speaking. Sometimes, we re-radiate, but as a last resort.

So now, if we've kept radiation on the side, if they are even that small group that does recur, we can still use radiation or chemoradiation if we choose to, so that group does particularly well. This is another study that's being done. There are new iterations of the robot that are coming out.

The first robot we began with was called a da Vinci Standard. I mean, that's the equivalent, back in 1991 when I arrived at Penn and the computer program was DOS. Then, we moved our way up to the first Windows program, which is a da Vinci S and now, there's the SI and the XI, which isn't used for transoral robotic surgery, but on the horizon is the da Vinci SP, which is a single port system in which small tools come out of one inch and a half port and give an even better access to the throat. So these are all exciting things on the horizon.

Dr. Lee Freedman:

Well, I very much want to thank Dr. Gregory Weinstein for educating us about transoral robotic surgery, relatively new technique, developed at Penn Medicine that has equal or improved efficacy over standard approaches and the ability to drastically reduce morbidity from other types of treatments that patients with this problem have negated in the past.

Again, Dr. Weinstein, thank you so much.

Dr. Gregory Weinstein:

You're very welcome. Thank you.

Moderator:

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