Scientists seek to perfect calculations for comparing cervical cancer radiation doses

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Research from VCU Massey Cancer Center has found that one of the standard practices for comparing cervical cancer radiation therapy treatments may be misleading, and the use of an alternative mathematical formula could be used to more effectively predict and potentially improve outcomes for patients.

Cervical cancer originates in the tissue connecting the uterus (or womb) to the vagina, and an estimated 12,820 new cases of the disease were diagnosed in 2017, according to the National Cancer Institute.

If cervical cancer is diagnosed at an advanced stage (anything greater than stage 1), the standard course of treatment is a combination of chemotherapy with 5-6 weeks of external beam radiation therapy, or radiation delivered from outside of the body, followed by brachytherapy, a form of targeted internal radiation therapy.

Brachytherapy for cervical cancer is primarily performed using a long, thin metal tube called a tandem applicator that passes through the cervix into the uterus and delivers radiation to the surrounding tissue. There are different types of tandem applicators, the main difference being the shape of the part that delivers the radiation.

About a decade ago, the standard for performing cervical brachytherapy was to administer radiation by placing an applicator inside a patient with a low-dose-rate radioactive source inside. The woman would then remain in the hospital for several days while the source of radiation decayed.

The radiation therapy was planned using x-rays, which can't clearly show the uterus or cervix and thus made targeting cancer difficult based on individual patient anatomy.

Over time, physicians have increasingly utilized computerized tomography (CT) scans, magnetic resonance imaging (MRIs) and volumetric planning to perform more personalized, high-dose-rate treatments that only take about 10-15 minutes to deliver, according to Emma Fields, M.D., radiation oncologist and member of the Developmental Therapeutics research program at Massey.

"What we've started doing is prescribing to what's called a D90, which basically means a dose covering 90 percent of the volume of the cervix. Around the country and around the world, we report based on D90, and we compare outcomes based on this as well," Fields said.

In an era of precision medicine where cancer treatment is being personally tailored to each individual patient, brachytherapy is largely characterized by heterogeneous dose distributions, meaning that varying levels of radiation are targeted more heavily in specific portions of the cervix based on the presence of cancerous cells.

"At Massey, what we're concerned about is that within practices and between practices we are assuming that patients' doses are all the same based on the D90 classification, when in fact the way we're customizing the brachytherapy treatments might be completely different. We're trying to determine a more precise mathematical equation to more accurately represent personalized treatment plans," Fields said.

A first study, led by Fields and published in the *International Journal of Radiation Oncology*, set out to determine if using the D90 classification was reliable to compare differing techniques, planning styles and applicator types when reporting the doses delivered with brachytherapy treatments.

Fields, along with a team of researchers from VCU, the London Health Sciences Centre in Ontario and the University of Colorado, compared cervical cancer brachytherapy treatments for patients from the three facilities using three different mathematical equations to categorize the doses of radiation applied to each patient's cervix:

1) The previously described D90, which is the minimum dose that covers 90 percent of the volume of the cervix,

2) Equivalent Uniform Biologically Effective Dose (EUBED), which accounts for the sensitivity and resistance of cells to radiation, and

3) Generalized Biologically Effective Uniform Dose (gBEUD), which takes into account hot and cold spots on the applicator (where hot spots refer to areas of higher concentrated radiation and cold spots refer to areas where there are lower levels of radiation).

The study found that although all of the patients were classified as having received a similar D90, many of their treatments looked completely different when represented using both the EUBED and gBEUD formulas.

"A radiation oncologist in California might say that a patient has a similar D90 to a patient of a radiation oncologist in Virginia and we would assume we are delivering comparable treatments. But in reality, we're not. D90 is not descriptive enough to give specifics of each customized plan," Fields said.

Imagine if you gave two people two pieces of paper equal in size and told them that 90 percent of the paper needed to be colored blue. One person might trace a colored pencil lightly across the entirety of the sheet of paper, while the other person might take that same colored pencil and trace lightly across the entire sheet, but add six or seven large, darkly shaded blue circles in random spots on the paper. It's fair to say that both pieces of paper would appear much different, but both would have met the given criteria. To compare this analogy to Fields' research findings: using the D90 concept, both sheets of paper would be considered the same, but using either EUBED or gBEUD, the sheets of paper are actually much different.

A second study, published in (abstract form) Brachytherapy, went a step further and reviewed the outcomes of former Massey cervical cancer patients when their treatments were calculated with these new mathematical formulas. The research found that using the gBEUD, which assesses areas of high dose or "hot spots" within the cervix, one can correlate dose delivered with brachytherapy treatments to patient outcomes. In fact, women with more "hot spots" or heterogeneity within the treatment plan had higher rates of both local control and survival from their disease.

"It makes sense that certain parts of the cervix should be receiving more concentrated levels of radiation for a more effective treatment. By comparing D90s, you cannot reliably see which patients receive different levels of radiation and there was no correlation with patient outcomes. However, using gBEUD, you might actually be able to predict which patients will live or die. This could potentially replace D90 and improve the way we treat women with cervical cancer," Fields said, adding that this new equation could also inform radiation oncologists as to which type of tandem applicator to use for different patients.

These findings need to be backed up by data from other medical facilities, and Fields said the next step is to compare cervical cancer patient outcomes using gBEUD from the University of Colorado, the London Health Sciences Centre in Ontario and additional collaborators.

"If we have a better understanding of how brachytherapy can be modified to deliver the best outcomes, then we'll be providing a better service for our patients," Fields said.

Provided by Virginia Commonwealth University

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