Why are we still in the 1950s regarding management of cancer of uterine cervix?

“You are where you are today because you stand on somebody's shoulders. And wherever you are heading, you cannot get there by yourself. If you stand on the shoulders of others, you have a reciprocal responsibility to live your life so that others may stand on your shoulders. It's the quid pro quo of life. We exist temporarily through what we take, but we live forever through what we give”– Vernon Jordan, in a speech at Howard University, 2002.

Within the last decade, there have been many changes in the concept of physical dosimetry for cancer of uterine cervix and in the understanding of the radiation biology of uterine cancer. It has been more than 70 years since Todd and Meredith[1] proposed in 1938, a system of dosimetry for brachytherapy of cancer of cervix. They proposed the dose to the region where the ureter crosses the uterine artery as a tolerance dose to the treatment. The region was represented by Point A. Since neither this region nor the external os could be visualized in the radiographs (the only available method for imaging during this period), 15 years later, in 1953, they modified the definition of Point A in relation to the flange of the uterine applicator, which is supposed to represent the external os. Thus, today, most of the dosimetry for cancer of uterine cervix is applicator-based rather than cervix- or tumor-based and the dose prescription is to Point A which is defined in relation to the flange of the uterine catheter. Though ICRU 38 (1985)[2] proposed a system for uniform reporting, the dosimetry was still based on Point A and not on tumor volume or extent. While GEC-ESTRO[3] recommends 3D image-based treatment planning, dose to Point A is accepted for reporting. At a time when the external beam therapy, which accounts for almost 85% of radiotherapy, uses more sophisticated techniques for tumor localization, why does the brachytherapy practice have to resort to an imaging system in which the anatomy or tumor cannot be visualized?

The work of Potter et al.[4] at Vienna and Narayan et al.[5] at Melbourne have shown that the Point A marked in relation to the flange, many times lies either inside the uterus or outside, thus, over-dosing or under-dosing the volume of interest as seen from magnetic resonance (MR) imaging. These could have contributed to the local failures or complications or late reactions.

Many centers use a simulator for imaging the applicators. In these practices, the patient is transferred after the insertion of the applicators, to the simulator room and then to the treatment room. In the case of high dose rate (HDR) treatments, this may happen for all 5 or 6 fractions. With the transfer of the patient from operating table to transport trolley, to the simulator table, back to trolley and then to the treatment table, the applicator position would have shifted from the original satisfactory applicator position and the dose prescription point (i.e., Point A) itself would have moved in relation to the anatomy. Moreover, if the applicator slips down, Point A itself, defined in relation to the applicator, would have shifted. These lead to unintended changes and errors in the dosimetry. Moreover, for intra-operative and intra-luminal brachytherapy, an HDR unit in the theatre with imaging modality will be extremely useful.

The best method to overcome these pitfalls is to use MR-compatible applicators, image, and plan for each treatment without moving the patient after application, treating the patient in the same position (of course this requires the installation of the HDR unit and the MR imaging facility in the theatre itself) and then removing the applicator. Hack[6] and Tanderup[7] also have reported on the improvement in dosimetry with MR imaging. Alternatively, one could install an Integrated Brachytherapy Unit (Nucletron). However, since this also images with X-rays, tumor, bladder, sigmoid loops, etc., cannot be visualized. With an abdominal ultrasound imaging with 5-7.5 MHz transducer, one could delineate the uterus for dosimetry. Further, erroneous perforation of the uterus can be avoided and the applicator can be centered in the uterus. With image-guided brachytherapy, the treatment volume could be defined and if necessary, prescription points could also be identified and marked (Narayan et al.[8]). With inverse planning, the isodose surfaces could be generated to fit the volume of interest. This will be a cheaper, but reasonably accurate method.

Even if MR/CT images are obtained earlier for External Beam Radiotherapy (EBRT), there could be radical changes in the tumor volume by the end of EBRT. Hence, instead of going by Federation of Gynecology and Obstetrics (FIGO) staging or tumor volume determined for EBRT, it
will be more appropriate to image during the intra-cavitary application and treat the volume of interest as seen at the time of insertion of the applicators. F-flurodeoxyglucose Positron Emission Tomography (FDG-PET) imaging provides physiologic information that is not provided by CT or MRI imaging. PET-CT imaging method also is being investigated. However, with this modality, it is not possible to visualize the sigmoid loops or other bowel parts.

An added advantage of imaging applicators in situ is that all necessary dose volume histogram (DVH) analyses could be done for GTV, critical tumor volume (CTV), tumor-bearing organ, and the adjacent organs at risk (OARs), and a most satisfactory plan could be generated for the treatment, thereby improving the overall outcome.

In addition to improvements in imaging and physical dosimetry, a few other factors may also be considered in view of the data pouring in on the understanding of tumor biology as mentioned in the beginning.

Prognosis Prediction Factors

Even with patients with similar clinical backgrounds in terms of staging, size, histology, etc., the clinical outcome could be different for same treatment regimen. Therefore, if using radiobiological methods the individual tumor sensitivity and response could be studied, a suitable RT regimen with appropriate chemotherapy could be generated individually. Another approach is immunohistochemical staining methods for DNA to analyze molecular characteristics of individual tumors and apply a clinical strategy for managing the outcome.

Growth Factors

A wide range of quiescent (G₀) cells have been observed in tumor with the same histology. The G₀ cells are relatively radiation-resistant and hence, play an important role in radiation response of tumor. Hence, a proper assessment of G₀ cells may help in altering the treatment modality.

Mitotic Index

It is reported that radiation may change the mitotic index of a proliferating cell population and an accelerated proliferation increases the dose required for complete cell control. A suggested strategy to reduce the effect of this acquired radiation resistance is to reduce the overall treatment time. Hence, with high MI proliferating cells, tumors frequently developed recurrence with RT alone for Ca.Cx.

Hypoxia

The existence of hypoxic cells is known as one of the factors affecting radiation resistance and as a possible cause of local failures in radiation therapy (RT). Pockets of hypoxic cells will also reduce effectiveness of chemotherapy. Some studies have shown that the re-oxygenation induced by irradiation plays an important role in the local control with RT for Ca.Cx.

Apoptosis and p53

It is well known that p53 plays an important role in radiation-induced apoptosis. In RT, occurrence of apoptotic cells after a total dose of 9 Gy has been associated with better pelvic control.

Molecular Targeting Agents

It may be possible to increase the radiation sensitivity of cancer cells by use of molecular targeting agent. For example, the epithelial growth factor receptor (EGFR) inhibition with antibody cetuximab in combination with RT has shown to increase tumor control and overall survival. However, others report that over-expression of the antibody was survival in RT patients. Some immunological factors have a definite role in intrinsic radiation resistance.

Heavy Ions

High linear energy transfer (LET) particles have various biological advantages in overcoming radiation resistance in tumors, such as decrease in oxygen enhancement ratio (OER) and decrease in lethal and sublethal damage repairs. Moreover, the use of the Bragg peak spread out in various degrees can cover tumor bulk and reduce the dose to OARs. Carbon ion therapy has shown improved results for Stage IIIIB and IVA cervical cancer patients in the clinical trials at National Institute of Radiological Sciences (NIRS) Chiba.

Host Reaction

The immunohistochemical results of the host anti-tumor immunity will be important apart from the radiation biology of the tumor. Lymphocyte infiltration into the tumor is known to influence the long-term survival.

Another thought in management of Ca.Cx. Various studies have shown that there is remarkable shrinkage in the tumor volume during the treatment. Hence, is it not feasible to reduce the volume for successive treatments. Moreover, is it necessary at all to treat the entire fundus end when mostly the tumor is in and around the cervix? Currently, partial breast irradiation is an accepted policy. Why not adopt partial uterus irradiation as required by tumor volume?

Though the biological factors mentioned above, can
modify the outcome in individual patients, current cost-benefit analysis prevents use of these factors in routine brachytherapy in almost all centers. Further, these thoughts are still controversial.

However, image-guided brachytherapy is practicable and affordable for most centers. The least costly practice with much improved outcome will be the use of abdominal ultrasound guided intra-cavitary brachytherapy. In any case, it is high time to break the tradition of Point A or applicator-based dosimetry in brachytherapy for cervical cancers and move on to image-guided adaptive brachytherapy with target-based dosimetry.

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