

IMRT, IGRT, and other high technology becomes standard in external beam radiotherapy: But is image-guided brachytherapy for cervical cancer too expensive?

With 528,000 new cases every year, cervical cancer is the fourth most common cancer affecting woman world wide; it is most not able in the lower-resource countries. Almost 70% of the global burden falls in areas with lower levels of development, and more than one-fifth of all new cases are diagnosed in India (GLOBOCAN 2013).^[1] Moreover, two-thirds of the cancers diagnosed in India are presented with advanced stages, which makes the management challenging.^[2]

Definitive radiation therapy and concurrent chemotherapy is the accepted standard of care. Brachytherapy (BT) is the essential part of definitive radiotherapy shown to improve overall survival. While results for two-dimensional X-ray-based BT have been good in terms of local control, especially for early stage disease; morbidity and local failures remain.^[3] Improvements in BT planning have more recently paved way for image-based BT with improved outcomes. Many new developments for the treatment of cervical cancer have been considered during recent years;^[4] however, the role of BT cannot be challenged by any of the new technologies, due to its ability to deliver very high dose to the tumor while sparing the surrounding critical organs.

Clinical Evidence and Rationale

In the last 2 decades, significant technological advances resulted in the use of imaging techniques for three-dimensional (3D) data acquisition, contouring for both target and various critical organs and to optimize treatment planning for BT applications.^[4] Various imaging modalities like ultrasound (US), computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET) scans have been explored. Among all the imaging modalities, MRI was identified as a gold standard for diagnosis and image-guided adaptive BT (IGABT).

The term “adaptive” here means that the treatment plan is adapted to a target volume, which is changing in time from diagnosis to each BT treatment. MR-based BT is practiced mainly in parts of Europe, few centers in the US and Asia and a couple of centers in India. As compared to robust 2D outcome data, it is still evolving with initial clinical data showing promising results. Pötter *et al.*, have published their single institutional experience with MRI BT, where they reported 3-year pelvic control rate of 96% for tumors 2–5cm in diameter, and 90% for tumors more than 5cm in diameter and on the same side reduction of side effects compared to historical series.^[5] This is being tested further in an ongoing multicentric study involving several institutes in Europe, USA, and Asia. Preliminary results of the retrospective retro EMBRACE trial and prospective EMBRACE trial also maintain the high expectations.

Although MR image-based BT in principle appears promising, it is not been widely accepted for clinical practice, due to various reasons such as large patient numbers, lack of resources especially imaging, lack of training/expertise and other financial constraints, which makes implementation of this technique very challenging in the developing countries including India.^[6,7] Nevertheless, with the successful implementation of 3D conformal radiotherapy (3DCRT), intensity-modulated radiotherapy (IMRT), and image-guided radiotherapy (IGRT) in routine clinical practice, there is a growing interest in image-based BT for cervical cancers in India. In the recent past, a lot of new technology was integrated in daily clinical routine for external beam radiotherapy (EBRT) in India. Intensity modulation, new beam delivery devices such as robotic radiosurgery, helical delivery, and IGRT have been integrated without or only limited clinical evidence. For most of the technologies, only theoretical planning studies are available. Why wasn't image-guided BT for gynecology, which has a proven clinical evidence, then not already integrated in all those centers?

This is even more striking, as often costs are named as a major limitation. It is unclear if the costs for a single CT, which is the standard for most external beam plans is really the main issue? Only recently, another cost/effect analysis showed benefit for image-guided cervical BT over simple radiograph-based approaches.^[8]

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In many countries, including India, private corporate hospitals have quickly embraced the advances in EBRT; however, the advances in BT have been largely neglected. At a time when the entire EBRT practice is largely dependent on imaging for tumor and organ delineation, daily setup verification and adaptive radiotherapy, it is unfortunate that BT practice has to settle down with an imaging modality based on two radiographs, where no tumor or organs at risk (OARs) can be visualized, but some surrogate bony landmarks. On the other hand, the government hospitals in India have been burdened with large patient volume of cervical cancer patients, that makes the BT practice very challenging and it is time to introspect and find feasible and practical solutions that can be implementable, which will largely benefit the patients belonging to the developing world.

The Role of Imaging

Although the evidence about MR imaging modality is quite promising, it cannot be implemented for every single patient or fraction due to the limited infrastructure. A more detailed consideration of cost effectiveness needs to be identified, also the feasibility of the combination of the well-established and robust conventional techniques (2D orthogonal radiographs) and newer imaging modalities (CT, MRI, and US) need to be identified. Solutions in optimizing the resources, especially imaging are needed, which is the weakest link in the non-implementation of image-based BT in countries which in principle can perform sophisticated treatment approaches, but have limited infrastructure resources.

In the recent times, conventional simulators have been gradually being replaced with CT simulators in India, both in the government and in private hospitals; and hence the use of CT images is increasing for BT planning. It is well-documented that CT images provide better soft tissue resolution and the doses to OARs could be accurately determined as compared to conventional orthogonal dosimeter.^[9] Although MRI is superior to CT for target volume delineation, studies have revealed that both CT and MRI modalities are adequate for OAR analysis.^[10] For the target, MRI remains the gold standard. However, there are many different alternatives to be considered. For certain tumor configurations, a detailed and standardized clinical examination combined with a delineation protocol for CT can improve the accuracy of dose optimization during treatment planning substantially. However, for complex topographies, MRI seems essential. Such an approach might not be based on an MRI for every single fraction, as subsequent fractions can be planned with CT.^[11] There are more combinations and clinical protocols should prioritize the need for MRI, CT, or even simpler methods based on the individual tumor characteristics.

US will certainly play an important role in the future.^[12,13] However, care should be taken that the proposed methods using trans-abdominal probes are finally 2D imaging techniques, mainly taking into account the thickness of tumors, while the width of the tumor, especially when infiltrating the parametrium might be better seen with trans-rectal probes, which can provide similar as for prostate BT 3D datasets. However, for these imaging techniques certain technological developments are necessary to track the position of the applicator in relation to US3D dataset, similar as the link between prostate template and US probe.

Applicator Selection

Conventionally, for cervix cancer BT, only intracavitary applicators were used, which produce dose coverage of 4cm in width at the level of point A. However, if the tumor is large, much more than 4cm at the level of point A at the time of BT, then, the dose coverage is inadequate if a standard intracavitary plan with prescription to point A is applied. Adaptations to larger volumes can partly be performed, but are limited to the fact that prescription to a larger volume will increase the dose to the OARs. By inserting interstitial needles through predefined holes in the ring applicator, the dose could be further shaped, allowing an increase of dose in the proximal to middle third of the parametrial space without significantly increasing the dose to the OARs.^[14] A similar applicator design is available for tandem-ovoid applicator type.^[15] IGABT mandates use of CT/MR compatible applicators that do not throw artifacts and interfere with the CT or MRI signal such that tumor visualization is possible. The applicators are made up of titanium/carbon material for CT/MR compatibility making them commercially expensive as compared to applicators made of stainless steel material. Indigenous development of these new applicators may reduce the cost to a large extent, and will make it affordable to the developing world. Countries like India, who has the expertise in the indigenous development, can take the lead in this direction.

Role of Physicist

As any other advanced techniques, image-based BT too requires systematic clinical implementation that includes familiarization of the processes. Inappropriate implementation of IGABT and change of clinical practice based on this could be damaging to the patients. In the past, lack of proper treatment planning system (TPS) quality assurance procedures has led to some serious accidents. Unlike treatment delivery errors, which are usually random in nature, the errors from the TPS and applicator commissioning are more often systematic and can be avoided. In image-based BT, there are new concepts in reconstruction, prescription, and optimization which needs to be adopted for uniform reporting. The

transition from point A based to high-risk clinical target volume (HR-CTV)-based optimization has been a big challenge. In addition, there is a lot of debate in the literature about the use of inverse planning for cervical cancer BT. At the moment, inverse planning is not widely used in clinics, and had to be done with caution as certain algorithms are known to produce large variation among the dwell times, it is important to understand how these algorithm works in a certain clinical situation.

It should be highlighted that the current state of the art concept of IGABT is more sophisticated than most external beam techniques. The target volumes are tracked at least from implantation to implantation, showing the need to adapt the dose distribution not only via dwell time optimization, but also via applicator optimization.^[16] The use of interstitial applicators in addition to intracavitary applicators increased the degree of freedom substantially. This allows more conformal dose distribution, in order to cover larger tumors, while significantly sparing OARs. The whole process belongs to the most sophisticated treatment approaches in radiotherapy. Planning aims as defined for each individual patient, based on the tumor characteristics including response during external beam. In order to reach these planning aims (dose constraints for target and OAR), an optimal implant geometry is planned, inserted (often with the use of image guidance via US), and planned optimization is performed on a TPSs. In most cases, the resulting plan is a compromise between target and OAR dose values, which is finally prescribed for the individual patient. Each patient gets an individualized and adapted treatment plan.

Uncertainties

With increasing conformity of dose, and the inherent property of BT of high dose gradients, it becomes important that the delivery of dose is in accordance with what is planned on the TPS. Optimal source geometry, timing, and stability are prerequisites for safe delivery of optimized BT. Both patient-related factors and technical issues associated with the BT equipment can give rise to uncertainties in the delivered dose. It is well-recognized that equipment-related quality assurance has to be conducted periodically to prevent the dose delivery errors. Patient-related factors are being identified as applicator displacement, organ motion, between the treatment planning and dose delivery.

However, what is finally missing is dose delivery verification as we have in EBRT, with portal imaging, cone-beam CT, and tools for off-line/on-line correction. In contrast to EBRT, in BT, we miss verification systems that provide the proof that the source reaches its planned position, or by mistake no transfer tubes were exchanged or any other variation in anatomy and applicator geometry. This will be the logical next step to be developed and

integrated. Research projects are focusing on innovative on-line imaging methods and appropriate *in vivo* dosimetry methods. After successful implantation, no other treatment modality will be able to deliver such high doses with such high accuracy. It is, especially, very important, that in addition to the management of variations, mistakes should be avoided. It is often seen in centers who start with IGABT, most focus is on the new planning methods, while the basic quality assurance is becoming of less importance. It is essential to perform appropriate commissioning and constancy checks.

Summary

CT-based planning should become the state of the art for this important cancer of female patients. There should be no debate about this, as every prostate patient is planned either with CT for EBRT or US for BT at least. However, the use of other imaging modalities, especially MRI as the gold standard, can be considered based on the individual case. Also new verification techniques might decrease the amount of reimaging needed for several fractions or implantations. As sophisticated and high tech modalities are more and more integrated into the clinical routine for EBRT, it should be the aim, to also implement most sophisticated methods for BT, especially on the basis of clinical evidence which was not always the case when integrating expensive equipment and techniques into EBRT.

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