Intracavitary Brachytherapy in Cervical Cancer: a Physics Perspective

Diana-Cristina Pop¹,², Viorica Magdalena Nagy¹,²

¹) “Prof.Dr.Ion Chiricuţă” Institute of Oncology Cluj-Napoca; 2) “Iuliu Hațieganu” University of Medicine and Pharmacy Cluj-Napoca, Romania

INTRODUCTION

By the early 1950s, after its discovery and implementation in medicine, brachytherapy (BT) had become a well-established modality of treatment. As it is today, intracavitary brachytherapy (ICBT) was used to deliver most of the central tumor dose for cervical cancer [1].

Because of the developments in external beam radiotherapy, allowing delivery of doses to deep tumors competitive with those achievable by BT, the role of BT was not secure in the 1950’s. The disadvantages of BT, such as the rigidity of applicators, the need of surgical skills for positioning and the exposure to radiation by personnel were clear to the radiation therapist and therefore BT was underused [2,3].

One of the first innovations in BT was the remote afterloading technology, introduced initially by Walstam and Henschke et al, in which sources are robotically transported from a shielded safe to their treatment position in the implanted applicators, and therefore sparing radiation exposure for the personnel.

For ICBT applications, the dose rate is one of the most important factors, because it refers to the level of “intensity” with which radiation is delivered. Cobalt-60 was one of the first artificial radionuclides used in ICBT, and because of its short half-life (5.26 years) it increased the complexity of the low dose rate (LDR) BT. Therefore with the half-life of 30 years Cesium-137 was used almost exclusively for LDR BT. In 1965 O’Connell et al introduced the high dose-rate (HDR) in which fractionated treatments lasting only a few minutes were administered. For HDR BT the most used radionuclide is Iridium-192 with a half-life of 73.8 days [1,4-6].

Regarding the BT planning for cervical cancer, the last 50 years have dramatically altered the clinical practice: computer isodose calculations, 3D imaging for defining target volumes and for applicator insertion guidance, and optimization of dwell weight and dwell time of the single-stepping source [7].

At its early age, BT was a purely surgical practice; this changed when developments in imaging were implemented in brachytherapy planning: from X-Ray radiographs to computed tomography (CT) and other 3D imaging modalities in interstitial and intracavitary [1,8-11].

MATERIALS

We searched on PubMed using combinations of terms, such as brachytherapy, cervical cancer, point A, 2D and 3D. From all the articles found, we considered eligible 34 English language articles written in the last 10 years.
CONVENTIONAL 2D BRACHYTHERAPY

In 2D, BT for cervical cancer treatment planning system uses two orthogonal radiographs which are taken with a conventional simulator, for applicator reconstruction and dose prescription to a point A. Point A as recommended by the Manchester system was originally defined as 2 cm superior to the lateral vaginal fornix and 2 cm lateral to the cervical canal (Khan) [12,13]. However, depending on the institutional protocols brachytherapy treatment for cervical cancer requires multiple applications which could lead to a variation in the applicator geometry and its spatial position in relation to the pelvic organs, pelvic bony anatomy and the organs at risk, and therefore position of point A is variable [14-19]. The International Commission on Radiation Units and Measurements (ICRU) Report 38 defined point A in relation to the applicator, 2 cm superior to the flange and 2 cm lateral from the axis of the applicator. Still multiple applications for one patient involves a variation in the applicator, resulting in a varying location of point A, and the reporting dose to point A becomes fraught with uncertainty [14,16,20,21].

Regarding the organs at risk (OARs) in cervical cancer, for 2D BT they are easily defined as points according to the ICRU 38 Recommendations[14,22], and it is imperative that the extent of tumor coverage within the prescribed dose would still remain ambiguous [14,23]. Moreover, the outcomes in cervical cancer have not been found to correlate with the point A doses. Katz et al, evaluated the outcomes for tumor control and bladder and rectal morbidity for 396 patients with respect to the dose at point A and also the ICRU Report 38 rectal and bladder points, and they reported a lack of correlation between the reference doses and outcomes [14,24].

A study shows that point A dose was a poor surrogate for a target dose with typical variations of the dose to the 90% (D90) of the high-risk clinical target volume (HR-CTV) between 60% and 150% of point A dose. Although point A could not predict the target dose in individual patients, it provided a reasonable estimate of the median HR-CTV D90, which indicate that point A is a good representation of “an average extension” of the tumor/cervix [25].

The technique used to define the prescription point A, the accuracy of rectum and bladder points position, the image quality of orthogonal radiographs and accuracy of applicator can also result in variations in doses to the OARs. In AP radiographs it is difficult to mark the rectum and bladder points and to identify the rectum points because the image of rectum marker could be superimposed with bladder marker and dummies inside the applicators. Also the accuracy of applicator reconstruction depends highly on the image of dummies identified in orthogonal radiographs. In lateral radiographs, the dummies inside the applicator are difficult to identify because of the thickness of pelvis’s tissues. The dose to bladder and rectum can also be various compared to the first fraction and the second fraction of treatment, therefore, the 2D brachytherapy treatment planning in evaluating the OAR doses can still be used as the ICRU reference points [12].

The advantage of the Manchester system point A prescription is the constancy of dose rate at point A, which was easily adopted in clinical practice on account of its simplicity and was most suitable with the limited availability of imaging modalities (i.e., orthogonal radiographs) [14].

The duration of cervical cancer ICBT is based on the dose rate calculated at point A, although the dose at the other points is taken into consideration in evaluating a treatment plan. With the availability of the treatment planning computers, most users of the Manchester system examine the isodose distributions in the frontal and sagittal planes in addition to obtaining dose at point A and at the same time dose to OARs. The simplicity and cost-effectiveness of radiograph-based 2D planning has ensured its continued applicability for dose reporting in BT [12,26]. Pötter et al in their research concluded that the outcome for cervical cancer could be further improved using image based brachytherapy for a highly individualized treatment planning based on the topography of the actual tumor and OARs [14,27].

Thus even if there are innovations in brachytherapy, in some cancer centers which do not have a computed tomography (CT) simulator or did not emerge with a 3D planning system, orthogonal radiographs are still being used for cervical cancer, taken with a conventional simulator. Meanwhile, the most frequent clinical complications of the treatments result from a high dose delivered to portions of the rectum and bladder that are in close proximity to the irradiation area. Applicator placement in ICBT is very important in order to keep the dose received by the critical organs as low as possible; therefore the dose received by these organs must be evaluated in order to avoid complications [12].

IMAGE-BASED 3D BRACHYTHERAPY

The limitations of orthogonal radiographs and dose prescriptions based on point A used in cervical cancer BT, has mandated the exploration of BT based on the actual position of the tumor and OAR’s in relation to the applicator. In the 90’s, the availability of CT and magnetic resonance imaging (MRI) scans have led to CT/MRI compatible applicators. [14,28]. The three dimensional (3D) image based ICBT in cervical cancer can visualize tumour and adjacent organs and provide improved target coverage, local control and reduced late toxicity [29,30]. Calculations of doses to points for OARs does not provide volumetric information and spatial relationship between the applicator and OARs. Inaccuracy in dose calculation and target coverage may occur due to the anatomical variation and tumor size, thus better local control and clinical outcome can be achieved with complete coverage of target [31].
In cervical cancer, evaluation of doses to bladder and rectum are crucial because of their close proximity to the cervix and 3D BT can optimize and individualize treatment planning for each patient. Previous studies have shown that CT based BT for treatment of cervical cancer is feasible and several guidelines for image based ICBT have already been published in the literature [32-35].

The comparison between 2D and 3D-CT based treatment planning is made to ascertain the potential benefit of target coverage, sparing of OARs and treatment outcome. Though MRI has been clearly established to be superior to any other imaging in cervical cancer for tumor delineation and adjacent soft tissue, MRI based treatment planning is not available in many institutions [29,36].

Charra-Brunaus et al studied the impact of using 3D CT image based BT outcomes in the treatment of cervical cancer, and reported that the true maximal doses to bladder and rectum were underestimated when compared to the ICRU Report 38 reference points for these OARs and represented the 90th and 95th percentile of the maximum doses to these organs respectively. They showed that the outcomes are clearly improved both in terms of local control rates and toxicity rates have been demonstrated with use of image based brachytherapy planning. Although it is has been shown that CT scans are adequate for contouring the OARs, the CT based contours could significantly overestimate the tumor width [14,37,38].

The current state of the art in 3D BT for cervical cancer is MRI based treatment planning. The Groupe Européen de Curiethérapie-European Society for Therapeutic Radiology and Oncology (GEC-ESTRO) published their detailed guidelines in 2005 and 2006 on the 3D image-based treatment planning in ICBT for cervical cancer [36,39]. The American Brachytherapy Society (ABS) has also framed their recommendations and adopted the GEC-ESTRO guidelines for contouring, image-based treatment planning, and dose reporting [40,41]. These guidelines provide recommendations for tumor delineation—gross target volume (GTV), HR-CTV, intermediate risk (IR) CTV and OARs (rectum, bladder, sigmoid colon, and any adjacent bowel loops). The dose reporting are based on 3D image based dosimetric evaluation of ICBT and these include the reference volume, TRAK, prescribed dose, point A dose, D90 CTV (dose in 90% of CTV), D100 CTV (minimum target dose), D100 GTV (minimum dose in GTV), V100 CTV (CTV volume receiving ≥ 100% of the prescribed dose) and dose volume parameters for OARs. The ABS guidelines provide dose limits for target and OARs for ICBT based on both radiographs and image based brachytherapy [14,42,43].

3D optimization is used to improve target coverage and decrease the dose to critical organs and compare with the 2D orthogonal radiograph based plan. Compared to the 3D volume dose, the prescription points overestimate the dose to the target volume. The underdosing was because of the inability of two channel applicators to cover volumes in the region of the cervix and vagina [43,44,45].

In cervical cancer treatments, the transition from 2D to 3D CT to 3D MRI based BT has been rapid. Radiation oncologists need to correctly interpret the MRI data before the delineation of the GTV and the HR-CTV [37,38]. GEC-ESTRO recommends to start with the standard method of prescription and then adjust the loading pattern and dwell times for optimization. The ABS recommends cautious use of optimization based exclusively on dose volume histogram parameters as changes in spatial dose distribution may be significant and if not carefully analyzed there may be unfavorable results [14,24,36,40,41,46]. Also doses to organs at risk vary depending on the calculation method, in some cases, final dose accuracy appears after the third fraction, indicating that simulation and planning may not be necessary in all fractions [47]. For the major OARs the dose to the volume of 0.1 and 2 cm³ of the major organs at risk (OARs), i.e. bladder, rectum and sigmoid, were suggested to be reported at time of BT. Dose constraints for these OARs have been reported and established for the rectum and bladder [36,39,48,49].

The GEC-ESTRO working group in their guidelines for the MRI for 3D image guided cervical cancer BT, y recommended pelvic MRI scanning prior to radiotherapy and at the time of ICBT with one MRI image. Multiplanar (transversal, sagittal, coronal and oblique image orientation) T2-weighted images with pelvic surface coils have been considered as the golden standard for delineating the topography of the tumor and the critical organs, while the use of complementary MRI sequences (e.g., contrast-enhanced T1-weighted or 3D isotropic MRI sequences) was considered as optional [50,51].

A standard loading pattern should be used as the starting point for MRI based optimization. Individual changes of active dwell positions and dwell weights are guided by a concept of DVH constraints for target and organs at risk [50].

Positron emission tomography-CT (PET-CT) has been used increasingly for initial tumor evaluation and also during follow-up in cervical cancer. PET-CT has also been explored for brachytherapy planning in cervical cancer, since it is superior to other modalities for ruling out any positive regional lymph node or distant metastasis, and the additional information could also be used to assess the target volumes for image based BT [50,52,53].

Despite of all new imaging modalities, cervical cancer BT is still widely based on 2D X-ray imaging, limited individualization, and prescription of dose according to point A. A common language has been developed that allows different BT traditions to communicate. Important steps and challenges in MRI-based image guided adaptive BT (IGABT) in cervical cancer have been investigated and described in several publications with regard to: contouring, applicator reconstruction, and dose optimization [54-57]. Based on the clinical experience collected so far, the MRI-based IGABT
approach is expected to have a major impact on the clinical outcome with a concomitant decrease in the rates of both local failure and morbidity [58]. With the introduction of an MRI-based target concept it is possible to move from prescription at point A to prescription of dose to a 3D target volume in terms of dose volume histogram (DVH) parameters. Furthermore, dose optimization can be performed based on MRI image guidance, whereby standard loading patterns are modified to come to an individually sculpted pear-shaped isodose which is tailored to target and organs at risk at the time of BT. In this process of moving from 2D (X-ray and standard loading) to 3D (MRI) target definition and dose optimization it is essential to relate the classical dose prescription and standard loading patterns to the new routes of 3D dose prescription and dose optimization [25,50].

A number of institutional reports on DVH parameters have been published so far [25,50,59]. This data reveal that there are considerable differences between different institutions in reported dose levels to both targets and OARs in cervical cancer. These differences are not yet well understood, but they are associated with a number of factors such as: prescribed dose, applicators, dose rates, and patient population (stage distribution). The great step forward with MRI-guided BT is that it has become possible to compare the doses of these different BT traditions [25,60,61,62].

There are several studies that have compared the dose prescription in 2D and 3D cervical cancer BT. Madan et al report that 100%, 95% and 90% of the target volume is receiving only 4.2±0.63, 4.6±0.56 and 4.9±0.56 Gy respectively, when we are prescribing 7 Gray to point A in the 2D plan; similar results were reported by Gao et al. [29,63]. Other studies have also reported suboptimal coverage of target by 2D radiotherapy based planning due to poor geometry and inadequate target coverage [64,65]. They observed that the mean volume of GTV that received the prescribed dose was higher in early stage disease as compared to advanced stage. Tyagi et al. compared ICRU point based planning with volumetric planning and concluded that bladder doses are underestimated by orthogonal film based method but rectal doses were found similar to doses to 2 cm³ of volumes [66]. George et al. reported that only for major toxicity all DVH parameters were predictors [67].

Regarding the use of image based BT and intensitymodulated radiotherapy, in cervical cancer it can also improve dose distribution in target volume and overdose to organs at risk [68]. Few studies have concluded that in centers where MRI based brachytherapy is not feasible due to logistic reasons, OARs and target may be contoured with CT which gives comparable results to MRI for dose volume estimation if clinical findings and baseline MRI findings are applied in contouring of CT images [69,70]. A descriptive survey of European brachytherapy practices observed that MRI is being used by 20% for planning in cervical cancer [71].

Early data for 3D planning has substantiated the potential improvements of 3D over 2D planning overcoming challenges in optimizing technique, reproducibility, uncertainties in target delineation, and the dosimetric planning processes. Several studies have compared the cervical tumor coverage and critical organ sparing by 3D image-based brachytherapy to doses delivered by 2D radiography-based brachytherapy. In addition to the well-established dosimetric advantages, 3D planning additionally offers clinical advantages including: confirmation of applicator placement, decreased critical OARs doses for patients with a small cervix, accounting for sigmoid colon dose, and improved coverage for large volume disease while maintaining critical organ dosimetry [27,50,51].

Despite the observed dosimetric and clinical benefits for cervical cancer image-based BT, many uncertainties and challenges remain. Applicator reconstruction is a challenge to quality assurance in image-based brachytherapy, although a number of reconstruction methods have been proposed. Many uncertainties remain because the reconstruction of source channels can generate both random and systematic errors in DVH parameters. Finally the steep dose gradients of BT dose distributions place increased hones on accurate contouring which is challenged by “grey zone” interpretation on MRI imaging and evaluation of tumor response changes [51,72].

One of the first studies to evaluate the cost-effectiveness (C/E) of 3D IGBT compared with conventional (2D) brachytherapy for locally advanced cervical cancer is from Hayeon et al. Their analysis demonstrates that 3D IGBT for locally advanced cervical cancer is economically reasonable compared with 2D conventional BT, at a cost of about $18,634 per quality-adjusted life-years (QALY) gained for CT planning and $27,774 per QALY gained for MRI-based planning. This C/E analysis is important to identify treatment techniques that improve outcomes at a reasonable cost, and Hayeon et al demonstrate that use of 3D IGBT with either cross-sectional imaging modality (CT or MRI) was cost effective [73].

CONCLUSIONS

The purpose of this article was to analyze the evolution of brachytherapy treatment planning parameters and their involvement in dose prescription in the treatment of cervical cancer. We conclude that although 2D techniques are still being used because of its availability, we consider that it is imperative for research to evolve to achieve the high standards that we find in external beam therapy for cervical cancer. Although MRI-based BT is considered to be the “golden standard” for cervical cancer, the use of CT in BT planning has already proved its benefits. Regarding costs, 3D BT has been proven to be expensive but for the future the standard would be image guided external and brachytherapy
with plan summation, which cannot be done without BT DVH and more information about the dose to the OAR’s than dose points.

In the near future we want to implement 3D BT for treatment of cervical cancer in our institution, taking into consideration the GEC-ESTRO and ABS recommendations.

References

29. Madan R, Pathy S, Subramani V, Sharma S, Mohanti BK et al. Comparative Evaluation of Two-dimensional Radiography and Three Dimensional Computed Tomography Based Dose-volume Parameters for High-dose-rate Intracavitary Brachytherapy of


58. Kapp KS, Stuecklschweiger GF, Kapp DS, Hackl AG. Dosimetry of intracavitary placements for uterine and cervical carcinoma: results
of orthogonal film, TLD, and CT-assisted techniques. Radiother Oncol 1992; 24: 137-146


64. Kim RY, Pareek P. Radiography-based treatment planning compared with computed tomography (CT) based treatment planning for intracavitary brachytherapy in cancer of the cervix: analysis of dose-volume histograms. Brachytherapy 2003; 2: 200-6


