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Cervical cancer brachytherapy

# Cervical cancer outcome prediction to high-dose rate brachytherapy using quantitative magnetic resonance imaging analysis of tumor response to external beam radiotherapy

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ABSTRACT

*Background and purpose:* In order to assess tumor regression and outcomes, a volumetric analysis was conducted for cervical cancer patients treated with magnetic resonance imaging (MRI)-based image-guided brachytherapy (IGBT).

*Materials and methods:* Consecutive patients with FIGO stage IB1–IVA cervical cancer receiving chemoradiation from 2007 to 2013 were identified, excluding patients with perineal template-based interstitial brachytherapy or without undergoing MRI. A ring and tandem applicator ± interstitial needles was used. T2-weighted imaging was completed following applicator insertion. Gross tumor volumes (GTVs) were retrospectively contoured: initial GTV ($GTV_{Pre\text{-}EBRT}$), GTV at first brachytherapy ($GTV_{IGBT}$) and percent residual GTV at first brachytherapy (% $GTV_{Residual}$).

*Results:* Eighty-four patients were identified. With 20.8-month median follow-up, two-year estimates of local control (LC), disease-free survival (DFS) and overall survival (OS) were 91.3, 79.8, and 85.0%, respectively. Multivariate Cox regression revealed adenocarcinoma (HR 5.88, $p = 0.03$) and $GTV_{IGBT}$ (HR 1.17, $p < 0.01$) as predictors for local failure. $GTV_{IGBT} > 7.5$ cc was associated with inferior 2-year LC (75.0 vs. 96.6%, $p < 0.01$), DFS (42.6 vs. 91.6%, $p < 0.01$) and OS (65.2 vs. 91.5%, $p < 0.01$). No difference in mean HRCTV $D_{90}$ $EQD_2$ was seen between the groups ($p = 0.61$).

*Conclusion:* Aside from known benefits of IGBT, MRI-based planning allows for assessment of tumor regression and prognosticates patients.



At present, the incidence of cervical cancer in the United States in 2014 is estimated to be 12,360 [1]. Despite the declining incidence of cervical cancer in the United States, overall 5-year mortality rates have held steady at approximately 1/3 since the mid-1970s [1]. Current standard treatment for locally advanced cervical cancer consists of external beam radiation therapy (EBRT) with concurrent chemotherapy and integrated brachytherapy [2,3]. Options for treatment upon disease recurrence have limited impact on survival, thus prognostic information obtained early during the treatment course when adjustments can still be implemented would have great utility [4,5].

During the last few years, image-guided brachytherapy (IGBT) has demonstrated superior outcomes to conventional brachytherapy in regard to local control and late toxicities [6]. Whereas 2-dimensional brachytherapy utilized a standard pear-shaped isodose configuration, IGBT using MRI, CT, and/or ultrasound has permitted three-dimensional treatment planning that is better able to optimize the dose to irregularly-shaped tumors [7,8]. Several studies have been performed over the last decade examining the utility of serial diagnostic MRIs throughout the treatment of cervical cancer to examine tumor regression and subsequent prognosis [5,9–13]. As part of the treatment planning protocol at our institution, MRI images are obtained both before the start of EBRT and at each fraction of IGBT for treatment planning, allowing the ability to radiographically assess treatment response. The goal of the current work is to determine whether non-diagnostic MRIs obtained with first fraction IGBT can help to prognosticate treatment outcome based on volumetric tumor response.

## Materials and methods

### *Patient population and treatment*

From 2007 to 2013, patients with biopsy-proven cervical cancer treated at Magee-Womens Hospital of UPMC were retrospectively identified. We included FIGO stage IB–IVA patients who were

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treated with concurrent cisplatin and external beam radiotherapy (EBRT) followed by high dose rate (HDR) intracavitary brachytherapy. Patients were excluded if they received surgery prior to initiation of EBRT, did not receive MRI scans both before and prior to or at the time of first brachytherapy application at our institution, or received perineal template-based interstitial brachytherapy.

### *Brachytherapy technique*

HDR $Ir^{192}$ brachytherapy using a ring and tandem approach with or without interstitial needles via a Vienna applicator (Nucletron, an Elekta company; Elekta AB, Stockholm, Sweden) was typically integrated starting in the fourth or fifth week of treatment (median 4.6 weeks, interquartile (IQ) range 4.3–5.1 weeks). Brachytherapy was delivered in 5 equal fractions of 5–6 Gy per fraction based on clinical response. Brachytherapy was given once weekly during EBRT and then twice weekly after completion of EBRT. Chemotherapy was not delivered on the same day to avoid potential toxicity. An MR-compatible Smit sleeve (Elekta) was inserted prior to and removed after brachytherapy. Following applicator insertion, patients underwent MRI imaging for treatment planning with subsequent volume-based optimization using either PLATO™ Brachytherapy Planning System, version 14.3 (Nucletron) or Oncentra® Brachy Planning System, version 4.3 (Elekta). Optimization and planning were completed following each applicator placement to account for changes in target volume size and organs-at-risk (OARs). Gross tumor volume (GTV), high-risk clinical target volume (HRCTV) and OARs (sigmoid, rectum, small bowel and bladder) were contoured for each fraction as per GEC-ESTRO guidelines [7,8]. Equivalent dose at 2 Gy ($EQD_2$) values were recorded for each fraction using an $\alpha/\beta$ ratio of 10 for tumor and 3 for normal tissue. Plan optimization parameters were as follows: HRCTV $D_{90} \geqslant 100\%$ of the prescribed dose per fraction (total $EQD_2$ 75–85 Gy), rectum $D_{2cc}$ $EQD_2 \leqslant 70$ Gy, sigmoid $D_{2cc}$ $EQD_2 \leqslant 70$ Gy, and bladder $D_{2cc}$ $EQD_2 \leqslant 85$ Gy incorporating EBRT and all fractions of brachytherapy. Priority was given to meet the HRCTV constraint first.

**Table 1**
Patient, disease and treatment characteristics ($n = 84$).

| Characteristic | *n* |
|---|---|
| Age (years) | |
| Median (range) | 48.5 (28–85) |
| FIGO stage | |
| IB1 | 7 (8.3%) |
| IB2 | 13 (15.5%) |
| IIA1 | 1 (1.2%) |
| IIA2 | 1 (1.2%) |
| IIB | 48 (57.1%) |
| IIIA | 0 (0.0%) |
| IIIB | 14 (16.7%) |
| Histology | |
| Squamous | 69 (82.1%) |
| Adenocarcinoma/adenosquamous | 15 (17.9%) |
| Grade | |
| Well-differentiated | 15 (17.9%) |
| Moderately differentiated | 19 (22.6%) |
| Poorly differentiated | 32 (38.1%) |
| Not reported | 18 (21.4%) |
| Clinical tumor size (cm) | |
| Median (IQ range) | 5.0 (3.5–6.2) |
| Lymph node status | |
| Positive | 42 (50.0%) |
| Negative | 42 (50.0%) |
| EBRT technique | |
| 3DCRT | 24 (28.6%) |
| IMRT | 60 (71.4%) |
| EBRT dose (Gy) | |
| Median (IQ range) | 45.0 (45.0–45.0) |
| Brachytherapy technique | |
| Ring and tandem | 78 (92.9%) |
| Vienna | 6 (7.1%) |
| Image-guided brachytherapy technique | |
| MRI | 47 (56.0%) |
| Hybrid CT/MRI | 37 (44.0%) |
| Brachytherapy dose (Gy) | |
| Median (IQ range) | 27.5 (27.5–27.5) |
| Total treatment time (weeks) | |
| Median (IQ range) | 7.1 (6.6–7.5) |
| Time to integration of brachytherapy (weeks) | |
| Median (IQ range) | 4.6 (4.3–5.1) |

*Abbreviations*: IQ = interquartile, FIGO = International Federation of Gynecology and Obstetrics, EBRT = external beam radiotherapy, 3DCRT = three-dimensional conformal radiotherapy, IMRT = intensity modulated radiotherapy, MRI = magnetic resonance imaging, CT = computed tomography.

### *Magnetic resonance imaging*

MRI scans were obtained prior to the initiation of EBRT (pre-EBRT MRI) and then at the time of the first brachytherapy application (IGBT MRI). All patients underwent image-guided brachytherapy; those treated prior to 2011 had MRI completed only with the first applicator placement and CT scans for each placement thereafter (CT/MR hybrid approach) [14,15]. Following this time period, patients underwent MRI with each applicator placement when possible. Scans were completed on a GE Signa HDx 1.5T MRI (GE Healthcare, Little Chalfont, United Kingdom), with a majority of patients undergoing T2-weighted 3D Cube™ sequence in order to rapidly acquire images with limited quality degradation. Pre-EBRT and IGBT MRIs were imported into Eclipse™ version 11.0 (Varian Medical Systems Inc., Palo Alto, California, USA) for volumetric measurements. Gross tumor volumes (GTV) were determined by contouring the tumor, identified by hyperintense signal on T2-weighted imaging, on each individual slice and summing the voxel volumes. Percentage of the residual gross tumor volume (% $GTV_{residual}$) was defined as the GTV at the time of first applicator insertion ($GTV_{IGBT}$) divided by the $GTV_{Pre\text{-}EBRT}$ multiplied by 100. To limit bias and interobserver variability, a single author completed all GTV contours retrospectively who was blinded to clinical examination findings and outcomes.

### *Outcomes and statistical analysis*

Statistical analysis was completed using IBM SPSS version 22.0 (IBM, Armonk, NY, U.S.A.). Local failure was defined as biopsy-confirmed recurrence along the cervix or adjacent pelvic organs including the vagina, parametria and uterus. Disease-free survival was defined by the lack of either local or distant recurrence. Kaplan–Meier analysis was used to estimate 2-year actuarial local control (LC), disease-free survival (DFS), and overall survival (OS). Log rank test and Cox proportional hazards modeling were used for univariate and multivariable survival analyses, respectively. ROC curve analysis and the Youden index (J) method were used to determine optimal cutoff values to define groups using the MRI volume parameters [16,17]. Logistic and probit regression were both conducted to model MRI volumetric data with the probability of local control.

## Results

Patient, disease and treatment details are provided in Table 1. Eighty-four patients were identified with a median age of 48.5 years. A majority had FIGO stage IIB disease (57.1%), most with squamous cell histology (82.1%) and equally divided regarding radiographic nodal status (50.0%). Median EBRT dose was 45 Gy (IQ range, 45–45 Gy) with most receiving IMRT (71.4%), while the median brachytherapy dose was 27.5 Gy (IQ range,