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Global Access to Radiation Therapy for Cervical Cancer: The Cost of Inaction

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physicians experienced in IMRT for the definitive treatment of cervical cancer in preparation for a collaborative NRG clinical trial.

Materials/Methods: A consensus working group that had participated in prior CTV definition was convened to contour on two treatment planning CT scans. Observers were blinded to the corresponding MRI scans. One case was an early cervical cancer and the other a loco-regionally advanced case. Clinical vignettes for the two cases were distributed and each participant was asked to draw CTV contours which included a CTV1 contour for the uterus/cervix and a CTV 2 contour for the vagina/parametria. Participants contoured on CT images of the pelvis using their own treatment planning software. Nodal CTV contours have been well described and were not included in this study. The CTV contours were then analyzed for consistency and clarity of target delineation using an expectation-maximization algorithm for simultaneous truth and performance level estimation (STAPLE, CERR), with Kappa statistics as a measure of agreement between observers.

Results: Contoured datasets were merged and analyzed for agreement. CTV1 contours showed almost perfect agreement (Kappa $>$ 0.8), while CTV2 showed moderate agreement (0.4 $<$ Kappa $<$ 0.6) among observers (see Table 1).

Abstract 28; Table 1

STRUCTURE MEASURE	Case 1		Case 2	
	CTV1	CTV2	CTV1	CTV2
Vol. Mean/Min/Max (SD in cc)	225.1/189.4/259.3 (22.4)	166.4/96.4/238.0 (49.4)	322.3/283.6/348.2 (21.1)	197.5/71.2/365.1 (75.3)
STAPLE/Intersection/Union Vol. (cc)	225.3/152.2/305.6	224.9/18.2/416.0	332.0/226.2/423.3	253.1/10.56/596.5
Kappa	0.82	0.56	0.87	0.50
Conformity Index (Mean Vol./Union Vol.)	0.74	0.40	0.76	0.33

Conclusion: Agreement among the experienced gynecologic radiation oncologists was excellent for CTV delineation in two representative intact cervical cancer cases. Consensus demonstrated near perfect agreement for the uterus and cervix and moderate agreement for the vagina and parametria. The variability seen in vaginal contours was primarily due to the vaginal length included in the CTV. The value of this data, building on previously published guidelines for IMRT in the post-operative setting and MRI guidance in the intact setting, provides clinically valuable information to promote safety and quality among radiation oncologists treating cervical carcinoma. Furthermore, this atlas will be used for future trials utilizing IMRT for the definitive management of intact cervical cancer.

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Phase 1 Trial of Bone Marrow Sparing Intensity Modulated Radiation Therapy With Concurrent Cisplatin and Gemcitabine in Stage IB-IVA Cervical Cancer

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Purpose/Objective(s): To determine the maximum tolerated dose (MTD) of gemcitabine (GEM) with concurrent weekly cisplatin (CIS) and bone marrow-sparing (BMS) IMRT in women with Stage IB-IVA cervical cancer.

Materials/Methods: Twenty-five women were enrolled in a phase I trial with IMRT (45.0-50.4 Gy in 25-28 fractions), CIS (40 mg/m^2 weekly) and escalating doses of GEM (50-125 mg/m^2 weekly) followed by HDR brachytherapy (25-30 Gy in 4-5 fractions) as indicated. No adjuvant chemotherapy was given. Cohorts 1 (50 mg/m^2; n = 6), 2 (75 mg/m^2; n = 5), 3 (100 mg/m^2; n = 3), and 4 (125 mg/m^2; n = 3) received CIS immediately followed by GEM, while cohort 5 (125 mg/m^2; n = 5) received GEM followed by CIS. Cohort 1E (n = 3) received extended field BMS-IMRT (EFRT) with concurrent CIS followed by 50 mg/m^2 GEM weekly. Primary IMRT sparing objectives were bone marrow (BM) (V_{10Gy} $<$ 90%, V_{20Gy} $<$ 75%) and bowel ($V_{45Gy}$$<$200 cc). Dose-limiting toxicity (DLT) was defined as grade 4 neutropenia lasting $>$7 days, neutropenic fever, grade 4 thrombocytopenia, symptomatic grade 3 thrombocytopenia, grade 3 or 4 non-hematologic toxicity (HT), or any treatment related morbidity causing a delay of therapy for $>$ 2 weeks, consistent with a prior GOG study (Rose et al., PMID: 17688925).

Results: Mean BM V_{10Gy}, V_{20Gy}, and mean dose were 82.6%, 63.4%, and 26.3 Gy, respectively. Mean bowel V_{45Gy} and mean dose were 180.5 cc and 26.5 Gy, respectively. DLTs occurred in cohorts 1 and 2 due to protracted nausea/vomiting, in cohort 5 due to grade 4 thrombocytopenia, and cohort 1E due to grade 3 infusion reaction. Acute grade $\geq$ 3 HT occurred in one patient within cohort 1, four patients within cohort 2, two patients each in cohorts 3 and 4, five patients in cohort 5, and three patients in cohort 1E. Acute grade $\geq$ 3 gastrointestinal (GI) toxicity occurred in one patient in cohort 1 and two patients each in cohorts 2 and 3. No patients treated with 125 mg/m^2 developed grade $\geq$3 acute GI toxicity. Overall, 18 of 25 patients developed grade 3 toxicity and 3 of 25 patients developed grade 4 toxicity. Six patients developed late grade $\geq$ 2 toxicity: radiation proctitis (n = 4), vesicovaginal fistula (n = 1), ureteral stricture (n = 1), and cystitis (n = 1). Another patient had a small bowel obstruction attributed to disease progression. With median follow-up of 16 months for patients without para-aortic disease, 1-year (2-year) overall survival was 100% (87.5%) and DFS was 93.3% (86.2%); one patient had LRF and two patients had distant metastasis.

Conclusion: With IMRT, concurrent CIS (40 mg/m^2) and GEM (125 mg/m^2) are feasible with clinically manageable toxicity. MTD in this study was not reached, and is higher than reported by Rose et al. Further study is needed to determine the MTD of GEM with EFRT and whether GEM/CIS sequencing affects toxicity.

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Global Access to Radiation Therapy for Cervical Cancer: The Cost of Inaction

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Purpose/Objective(s): Radiation therapy (RT) is a highly effective and curative treatment for patients with invasive cervical cancer, and is the standard of care for locally advanced disease. Although RT can be successfully delivered in developing countries, major gaps in access have resulted in substantial preventable morbidity and mortality, where nearly 90% of cervical cancer deaths occur. These gaps are multifactorial, but assumptions about excessive cost of RT in these regions preclude effective implementation. Using methodology developed for the Global Task Force on Radiotherapy for Cancer Control (GTFRCC), we examined the validity of these assumptions for the treatment of cervical cancer with external beam radiation (EBRT) and brachytherapy (BT) in upper middle-income income (UMIC), lower middle-income (LMIC) and low-income countries (LIC).

Materials/Methods: Based on the GTFRCC evidence-based estimation approach, we assumed that 71% of cervical cancer patients would require RT, with a mean of 21 EBRT and 3 HDR BT fractions per course, resulting in a 20% overall survival benefit. We developed a decision-analytic Markov model to assess three RT capacity scenarios from 2015 to 2035: 1) no increase in capacity; 2) linear scale-up from baseline coverage in 2015 to universal accessibility by 2035; and 3) immediate full availability. Model outcomes included total life years (LYs) and economic productivity (US Dollar). Costs, based on the GTFRCC efficiency model, and benefits were discounted by 3% annually over a lifetime horizon.

Results: If no action is taken to shift current RT capacity to universal accessibility, we project a loss of up to 21.4 million (M) LYs and $271.3 billion (B) due to cervical cancer alone over the next 20 years. Based on a realistic linear investment model, RT yields an additional 9.8M LYs (2.9M in LIC, 4.7M in LMIC, and 2.2M in UMIC) over 20 years, a $53.2B net increase in economic productivity ($2.6B in LIC, $16.4B in LMIC, and $34.2B in UMIC), and a broader societal net gain of $137.5B ($10.3B in LIC, $44.8B in LMIC, and $82.4B in UMIC). The additional investment necessary for HDR brachytherapy, an essential component of curative treatment, was only 5.5% greater than EBRT alone.

Conclusion: The failure to ensure global availability of EBRT and BT to treat cervical cancer would result in enormous human and economic consequences over the next two decades. This loss would occur before the benefits of primary cancer prevention strategies, such as HPV vaccination, are realized. The present study demonstrates that a realistic investment strategy over the next 20 years may yield a net economic benefit of up to $150B USD and potentially further benefits beyond that point in time. These findings support the value of scaling-up of EBRT and BT to treat cervical cancer and help to justify their inclusion in national cancer control planning.

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Total Treatment Duration for Cervical Cancer: Is 55 Days Still the Goal in the Era of Concurrent Chemotherapy?

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Purpose/Objective(s): Prior studies have demonstrated the importance of treatment duration (TD) in the management of cervical cancer treated with radiation therapy (RT) for both locoregional control and overall survival (OS). Most of the data support a 55-day goal for completion of all RT; however, this is largely based on treatments with RT alone. This study uses a contemporary national cohort treated with concurrent chemoradiation to determine the time point by which completion of RT is most critical.

Materials/Methods: The National Cancer Data Base (NCDB) was queried for all women with non-metastatic invasive cervical cancer diagnosed from 2004 to 2013 who underwent chemoradiation with external beam RT and brachytherapy. To calculate the optimal TD, we randomly divided the cohort into training and validation cohorts with preservation of the overall TD distribution. The training set included 5685 women, and the validation set included 5683. Bootstrapping was performed to generate 1000 simulated training sets for which the recursive partitioning analysis (RPA) algorithm was used to determine the optimal cut point of TD in each set to maximize separation in survival. We restricted RPA to generate only one cut point based on TD. The mean of the bootstrapped cut points was taken forward to validation. The Kaplan-Meier method was used to estimate 5-year OS in the validation cohort by defining two groups based on the determined cut point and compared using the log-rank test. To describe the entire cohort, a multivariate Cox proportional hazards model was generated.

Results: A total of 11,368 women were included in the study with a mean TD of 57.6 days and median TD of 54 days. The mean of the bootstrapped TD cut points generated by RPA was 65 days (standard deviation 7 days). In the validation set, 5-year OS was 68% (95% CI 66-69%) for those with a TD less than 65 days and 57% (95% CI 55%-61%) for those with a TD of 65 days or longer ($P < 0.001$). For the entire cohort on multivariate analysis, younger patient age, more recent diagnosis, geographic region, metro location, non-government insurance, lower Charlson/Deyo comorbidity, squamous cell carcinoma, earlier stage, negative lymph nodes, and TD less than 65 days were significantly associated with longer OS. After adjusting for these covariates, TD less than 65 days remained significantly associated with longer OS (HR 0.80 [95% CI 0.74-0.87], $P < 0.001$). By comparison, with adjustment, TD less than 55 days also was associated with OS but had less separation (HR 0.90 [95% CI 0.83-0.97]).

Conclusion: Shorter time to completion of radiation therapy is associated with longer survival in women with cervical cancer receiving chemoradiation and should be a goal in treatment. We found the maximally differential cutoff to be 65 days, slightly longer than the recommended time of 55 days.

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The Influence of Hospital Volume on Disease Outcomes of Advanced Uterine Cervical Cancer Patients: A Nationwide Cohort Study of Taiwan

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Purpose/Objective(s): To investigate the correlation between hospital volume and clinical outcomes in locally advanced cervical cancer patients treated with curative chemoradiation therapy or radiation therapy alone.

Materials/Methods: In this population-based retrospective cohort study, total 8,968 patients diagnosed of FIGO stage I to IV uterine cervical cancer from January 2007 to December 2013 were recorded in the Taiwan National Health Insurance Research Databases. This study examined the women who were treatment-naïve before and received curative radiation