Title

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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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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