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).

<table>
<thead>
<tr>
<th>STRUCTURE MEASURE</th>
<th>Case 1</th>
<th>Case 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vol. Mean/Min/Max</td>
<td>CTV1</td>
<td>CTV2</td>
</tr>
<tr>
<td>(SD in cc)</td>
<td>225.3/189.4/224.9</td>
<td>166.4/96.4/225.1</td>
</tr>
<tr>
<td>Kappa</td>
<td>(22.4)</td>
<td>(49.4)</td>
</tr>
<tr>
<td>Conformity Index (Mean)</td>
<td>0.74</td>
<td>0.56</td>
</tr>
<tr>
<td>Vol./Union Vol.</td>
<td>0.40</td>
<td>0.76</td>
</tr>
</tbody>
</table>

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 IMRT, concurrently with CIS and GEM, will be used for future trials utilizing IMRT for the definitive management of intact cervical cancer.


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 1 trial with IMRT (45.0-50.4 Gy in 25-28 fractions), CIS (40 mg/m2 weekly) and escalating doses of GEM (50-125 mg/m2 weekly) followed by HDR brachytherapy (25-30 Gy in 4-5 fractions) as indicated. No adjuvant chemotherapy was given. Cohorts 1 (50 mg/m2; n = 6), 2 (75 mg/m2; n = 5), 3 (100 mg/m2; n = 3), and 4 (125 mg/m2; n = 3) received CIS immediately followed by GEM, while cohort 5 (125 mg/m2; n = 5) received GEM followed by CIS. Cohort 1E (n = 3) received extended field BMS-IMRT (EFRT) with concurrent CIS followed by 50 mg/m2 GEM weekly. Primary IMRT sparing objectives were bone marrow (BM) (V100Gy < 90%; V20Gy < 75%) and bowel (V45Gy < 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 V100Gy, V20Gy, and mean dose were 82.6%, 63.4%, and 26.3 Gy, respectively. Mean bowel V45Gy 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 infusional reaction. Grade 3 or 4 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. Grade 3 or 4 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/m2 developed grade 3 or 4 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 >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/m2) and GEM (125 mg/m2) 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.


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 the Role of Radiation Therapy 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 ($16.4B in LMIC, and $34.2B in UMIC), and a broader societal net gain of $137.5B ($10.3B in LIC, 4.7M in LMIC, and 2.2M in UMIC) over 20 years, a $53.2B net increase in economic productivity ($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.