Title
Computed Tomography Consensus Clinical Target Volume Contouring for Intensity Modulated Radiation Therapy in Intact Cervical Carcinoma.

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Authors
Yashar, CM
Petersen, IA
Bosch, WR
et al.

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overall survival, the secondary endpoint was treatment-related acute hematologic toxicity.

Results: From October 6, 2008 to May 16, 2012, we enrolled 82 patients. The number of patients with stage IB2, IIA2, IIB, IIA and IIBB were 9, 7, 47, 2, and 28, respectively. Twenty-one patients (25.6%) had cervix tumor residual at the end of WPETRT. However, all patients achieved a complete tumor response at the last treatment of brachytherapy. With a median follow-up of 70.6 months (range, 53.0-89.0), the 1, 3, and 5-year cumulative overall survival rates (OSR) for the whole group were 87.8%, 86.5%, 83.3% and 83.3%, respectively. The 5-year OSRs for patients with stage I, II and III were 85.5%, 84.4% and 78.9%, respectively. During treatment, the incidences of grade 1-4 acute leucopenia were 89.6%, 62.3%, 11.7% and 0%, respectively, and the incidences of grade 1-4 acute granulocytopenia were 55.0%, 32.5%, 3.9%, 0%, respectively. The cumulative late complication rates were 4.8% (4 patients) for all grades; 1.2% for grade 1, 3.6% for grade 2. No grade 3 or higher late complications were observed.

Conclusion: Concurrent chemoradiation therapy with weekly cisplatin at 30mg/m2 and paclitaxel at 45 mg/m2 demonstrated excellent antitumor activity with tolerable hematologic toxicity for locally advanced cervical cancer patients. Based on these findings, we have initiated a prospective randomized phase III clinical trial to compare this regimen with standard weekly CDDP for locally advanced cervical cancer treated with CCRT.

Author Disclosure: L. Xie: None.

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Phase 2 Multicenter Clinical Trial of Bone Marrow—Sparing Intensity Modulated Radiation Therapy With Concurrent Cisplatin for Stage IB-IVA Cervical Cancer


Purpose/Objective(s): To test the hypothesis that intensity modulated radiation therapy (IMRT) reduces acute hematologic and gastrointestinal (GI) toxicity for patients with stage IB-IVA cervical cancer undergoing chemoradiation therapy.

Materials/Methods: We enrolled patients age ≥ 18 with stage IB-IVA cervical cancer on a single-arm phase II trial at 6 centers. All patients received 5-6 weekly cycles of cisplatin (40 mg/m2) concurrently with once daily IMRT (45.0-50.4 Gy in 25-28 fractions to the pelvis; gross nodes received up to 59.4 Gy simultaneously), followed by intracavitary brachytherapy as indicated. All centers underwent IMRT credentialing and centralized quality assurance review. Intensity modulated RT plans were designed to minimize radiation dose to the pelvic bone marrow, bowel, bladder, and rectum, while maintaining target coverage. The primary endpoint was the occurrence of either acute grade ≥ 3 neutropenia or clinically significant GI toxicity (grade ≥ 2 diarrhea requiring intravenous fluids and/or combination opiate/anticholinergic anti diarrheal medication) within 30 days of completing chemoradiation therapy. A pre-planned subgroup analysis was designed to test the hypothesis that PET-guided bone marrow-sparing IMRT (IG-BMS-IMRT) lowers the risk of acute neutropenia. Toxicity grading was according to NCI CTCAE v4. The trial is registered (NCT01554397).

Results: From October 2011 to April 2015, we considered 91 patients, with 8 screen failures and 83 eligible for analysis (86% were FIGO stage IIB-IVA). Median follow-up was 16 months. The incidence of any primary event was 26.5% (95% CI, 18.2-36.9%), significantly lower than the 40% incidence hypothesized a priori from historical data (2-sided t-test P = 0.007). The incidences of grade ≥ 3 neutropenia and clinically significant GI toxicity were 19.3% (95% CI, 12.2-29.1%) and 12.1% (95% CI, 6.7-20.8%), respectively. The incidences of any grade ≥ 3 hematologic and grade ≥ 2 GI toxicity were 38.6% (95% CI, 28.8-49.5%) and 42.2% (95% CI, 32.1-52.9%), respectively. Compared to patients treated without IG-BMS-IMRT (N = 48), patients treated with IG-BMS-IMRT (N = 35) had significantly lower grade ≥ 3 neutropenia (8.6% vs. 27.1%, 2-sided chi-square P = 0.035), and non-significantly lower grade ≥ 3 leukopenia (25.7% vs. 41.7%, P = 0.13) and any grade ≥ 3 hematologic toxicity (31.4% vs. 43.8%, P = 0.26). The 18-month disease-free survival and overall survival were 86.6% (95% CI, 78.1-95.9%) and 98.5% (95% CI, 95.5-100%), respectively. The 18-month cumulative incidences of locoregional failure, distant metastasis, and grade ≥ 3 late toxicity were 7.2% (95% CI, 3.6-10.8%), 5.0% (95% CI, 2.1-7.8%), and 8.9% (95% CI, 5.0-12.9%), respectively.

Conclusion: Intensity modulated RT reduces acute toxicity compared to standard treatment, with promising outcomes in the international population. IG-BMS-IMRT reduces the risk of acute neutropenia. A Phase III trial of IG-BMS-IMRT versus standard of care is warranted.


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Computed Tomography Consensus Clinician Target Volume Contouring for Intensity Modulated Radiation Therapy in Intact Cervical Carcinoma

C.M. Yashar,1 I.A. Petersen,2 W.R. Bosch,3 K.V. Albuquerque,4 S. Beriwal,5 J.P. Chino,6 B.A. Erickson,7 J. Feddock,8 D.K. Gaffney,9 R. Iyer,10 A.H. Klopp,10 C. Kunos,11 J.S. Mayadev,12 L. Portelance,13 A.N. Viswanathan,14 A.H. Wolfsinn,15,16 A. Jhingran,17 and L.K. Mell1

1University of California, San Diego, La Jolla, CA, 2Mayo Clinic, Rochester, MN, United States, 3Washington University School of Medicine, St. Louis, MO, 4University of Texas Southwestern Medical Center, Dallas, TX, 5Department of Radiation Oncology, University of Pittsburgh Cancer Institute, Pittsburgh, PA, 6Duke University Medical Center, Durham, NC, 7Department of Radiation Oncology, Medical College of Wisconsin, Milwaukee, WI, 8University of Kentucky, Lexington, KY, 9University of Utah Huntsman Cancer Hospital, Salt Lake City, UT, 10MD Anderson Cancer Center, Houston, TX, 11SUMMA Physicians, Akron, OH, 12University of California Davis Comprehensive Cancer Center, Sacramento, CA, 13Radiation Oncology Department, University of Miami/ Sylvester Comprehensive Cancer Center, Miami, FL, 14Harvard Medical School, Boston, MA, 15University of Miami Miller School of Medicine, Miami, FL.

Purpose/Objective(s): The primary endpoint was the occurrence of either acute grade ≥ 3 neutropenia or clinically significant GI toxicity (grade ≥ 2 diarrhea requiring intravenous fluids and/or combination opiate/anticholinergic anti diarrheal medication) within 30 days of completing chemoradiation therapy. A pre-planned subgroup analysis was designed to test the hypothesis that PET-guided bone marrow-sparing IMRT (IG-BMS-IMRT) lowers the risk of acute neutropenia. Toxicity grading was according to NCI CTCAE v4. The trial is registered (NCT01554397).

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

<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></td>
<td></td>
</tr>
<tr>
<td>STAPLE/Intersection/Union Vol. (cc)</td>
<td>225.3/152.2/224.9/18.9</td>
<td>332.0/226.2/253.1/0.56</td>
</tr>
<tr>
<td>Kappa</td>
<td>0.82</td>
<td>0.56</td>
</tr>
<tr>
<td>Conformity Index (Mean)</td>
<td>0.74</td>
<td>0.40</td>
</tr>
<tr>
<td>Vol./Union Vol.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Conclusion: Agreement among 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.


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 chemotheraphy 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 following by 50 mg/m2 GEM weekly. Primary IMRT sparing objectives were bone marrow (BM) (V10Gy < 90%; V20Gy < 75%) and bowel (V40Gy < 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 V10Gy, V20Gy, and mean dose were 82.6%, 63.4%, and 26.3 Gy, respectively. Mean bowel V40Gy 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 ≤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 ≤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/m2 developed grade ≤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 ≥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.


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

D. Rodin,1 T.P. Hanna,2 E. Burger,2 E. Zubizarreta,3 M.L. Yap,5 M.B. Barton,5 R. Atun,5 F. Knaul,5 J. Van Dyk,5 Y. Lievens,10 M. Gospodarowicz,1,11 D.A. Jaffray,12,13 and M. Milosevic1,14

1Department of Radiation Oncology, University of Toronto, Toronto, ON, Canada, 2Queen’s University, Kingston, ON, Canada, 3Harvard School of Public Health, Center for Health Decision Science, Boston, MA, 4International Atomic Energy Agency, Vienna, Austria, 5Ingham Institute for Applied Medical Research, University of South Wales, Liverpool, Australia, 6University of New South Wales Australia, Sydney, Australia, 7Professor of Global Health Systems, Harvard School of Public Health, Boston, MA, 8Miller School of Medicine, University of Miami, Miami, FL, 9Departments of Oncology and Medical Biophysics, University of Western Ontario, London, ON, Canada, 10Department of Radiation Oncology, Ghent University Hospital, Ghent, Belgium, 11Radiation Medicine Program, Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada, 12Radiation Medicine Program, Princess Margaret Cancer Centre.