Phase II study on the feasibility of Intensity Modulated Radiation Therapy (IMRT) in a multi-institutional setting for post operative concomitant chemoradiation for patients with cervical cancer. NRG Oncology/RTOG 0418. Primary and Secondary endpoint results.

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SUMMARY

NRG/RTOG 0418 was a phase II clinical trial designed to test the transportability of pelvic intensity modulated radiation therapy (IMRT). It was a landmark study which paved the ground for a national collaborative group randomized control trial comparing pelvic IMRT to standard pelvic radiation. The primary and secondary endpoint analyses with five years of follow up for patients treated on the cervical cancer arm are presented.

ABSTRACT

Purpose: To determine the transportability of post-operative pelvic IMRT for cervical cancer patients to a multi-institutional setting and to test the hypothesis that there is a reduction in acute bowel adverse events (AEs) compared to conventional techniques. In addition, the rates of local-regional failure (LRF), para-aortic failure (PAF), distant failure (DF), disease-free (DFS) and overall survival (OS) were estimated and chemotherapy compliance documented.

Methods and Materials: Patients who underwent surgery for cervix cancer and required adjuvant chemoradiation therapy were eligible. A dose of 50.4 Gy in 28 fractions to the nodal planning target volume (nPTV) and the vaginal PTV (vPTV) was delivered using pelvic IMRT. All patients also received weekly cisplatin. Tools to measure the quality of the radiation technique were developed and the ability of various sites to perform IMRT per guidelines was measured. OS and DFS were estimated with Kaplan-Meier, and LRF, PAF, and DF with cumulative incidence methods.

Results: Forty-eight patients were enrolled, of which 40 were eligible. For the nPTV and vPTV, 22 (55%) and 17 (42.5%) of the dose coverage were per protocol and 18 (45%) and 23 (57.5%) were within acceptable variation. Nine patients (22.5%) developed grade ≥ 2 acute bowel AEs and the chemotherapy compliance rate was 80%. The estimated five-year rates of LRF, PAF, and DF were 7.9% (95% confidence interval [CI]: 2.0%, 19.3%), 5.6% (CI: 1.0%, 16.6%) and 13.5% (CI: 4.8%, 26.6%), respectively. The estimated five-year DFS and OS rates were 83.9% (CI: 67.6%, 92.4%) and 92.1% (CI: 77.4%, 97.4%), respectively.

Conclusion: This phase II study has proven that pelvic IMRT is transportable to a multi-institutional clinical trial setting when adequate quality control tools are used. Compared to

historical data, pelvic IMRT is associated with a lower rate of acute gastrointestinal toxicity, better chemotherapy compliance and comparable disease control.

Key Words: Cervix cancer, Intensity Modulated Radiation Therapy, Combined chemoradiotherapy.

INTRODUCTION

While radiation therapy (RT) plays an important role in the management of patients with advanced cervical cancer, surgery is the preferred treatment option for young women with early disease1. Surgery has the advantage of allowing for ovarian preservation in premenopausal women and is thought to be associated with a lower rate of dyspareunia. In patients with intermediate risk factors (including presence of lymphovascular invasion, deep stromal invasion, tumor of more than 4 cm), adjuvant RT is indicated to decrease loco-regional recurrences [2, 3]. When higher risk factors are identified (i.e. positive pelvic nodes, positive resection margins or microscopic parametrial invasion), adding chemotherapy to adjuvant pelvic radiation leads to improved disease-free survival (DFS) and overall survival (OS)[4]. The superiority of a combined chemoradiotherapy approach (CRT) has also been proven for cervix cancer patients treated with a curative intent [5,6,7,8,9] . The combination of surgery and pelvic radiation or CRT is however associated with significant toxicity [2,3,4,10,11,12]. In the intergroup randomized trial, published by Peters et al [4], 40% of the patients treated in the CRT arm developed grade 2-4 diarrhea or small bowel obstruction. In addition, in the 122 patients assessable in the CRT arm, 27 episodes of grade 4 toxicity were reported (22%, grade 4 toxicity). Most of those episodes were related to hematologic toxicity. Only 60% of the patients randomized to CRT completed the chemotherapy treatment as planned. The chemotherapy regimen used in this collaborative group study was cisplatin 5-FU for four cycles. The chemotherapy regimen which was selected for the phase II study presented here was weekly cisplatin. A practice pattern analysis done among members of the Gynecologic Cancer Intergroup (GCIG) confirmed that this is the chemotherapy regimen most frequently used [13].

The role of pelvic intensity modulated radiation therapy (IMRT) in the treatment of patients with gynecologic cancer as a method to minimize gastrointestinal (GI), genitourinary (GU), and bone marrow toxicities was the subject of several publications [14, 15,16,17,18,19,20,21]. Dosimetric studies have reported up to a two-fold reduction in the dose delivered to the small bowel and reduction of 23% in the volume of rectum and bladder receiving the prescribed dose [14,15,16,17]. Single institution prospective studies on the use of pelvic IMRT for patients with gynecological tumors confirm the dosimetric studies results [18,19,20,21].

Other planning strategies (prone positioning, belly board [22,23]) could be used to decrease bowel toxicity from pelvic radiation. However, traditional radiation treatment techniques do not allow for sparing of critical structures that push into a target with a concave surface[24]. IMRT has this ability and therefore it seems to be the most suitable approach to minimize the dose to bowel loops filling the pelvic space after any type of hysterectomy (Figure 1).

IMRT involves complex treatment planning; it requires a significant amount of resources and specific training [24,25,26]. Its implementation could only be justified by sound data supporting its superiority over standard pelvic radiation. NRG/RTOG 0418 was a phase II trial designed to determine the feasibility of doing a multi centric clinical trial where pelvic IMRT would be used in a population of patients with gynecological cancer after surgery. The trial was designed to separately study results from the endometrial cancer and cervical cancer patients. The primary and secondary endpoint results for the cohort of patients enrolled on the cervical arm are presented here.

The primary endpoint of this study was to test the transportability of pelvic IMRT to a multi institutional clinical trial setting. Secondary endpoints also presented include the rate of grade ≥ 2 short-term bowel adverse events (AEs); the rate of chemotherapy compliance; and the

assessment of disease control in terms of local-regional failure (LRF), distant failure (DF), DFS, and OS.

METHODS AND MATERIALS

Patients

Patients with cervical cancer eligible for the trial had undergone surgery (either radical hysterectomy, total abdominal hysterectomy, vaginal hysterectomy or laparoscopic assisted vaginal hysterectomy) and were found to have positive pelvic lymph nodes, microscopic parametrial invasion, or two of any of the following criteria: presence of lympho-vascular invasion, tumor invading more than the superficial one third of the stroma, or tumor 4 cm or more in diameter. Patients who had undergone a simple hysterectomy were also eligible providing that lymph node involvement was ruled out by adequate imaging modalities. Patients had to be $\geq$ 18 years old, have a good Zubrod performance status (0-1), and have a normal complete blood count as well as normal renal and liver function at the time of enrollment. As no allowance was made for a boost to sites of residual disease, patients with microscopic disease present <3 mm from resection margins were not eligible. Patients diagnosed with papillary serous, clear cell or neuroendocrine histologies were also not eligible. Enrollment had to take place within seven weeks post-surgery. To be allowed to enroll patients on this protocol, each institution had to be credentialed for pelvic IMRT. Credentialing included successful completion of a phantom dosimetry study submitted to the Image Guided Therapy Center (ITC). All institutions participating in the protocol obtained approval from their local internal review board and all patients were enrolled on the trial after signing an informed consent.

Simulation, Contouring and Treatment planning

For each patient, two simulation CT-scans were done one with a full bladder and a second one with empty bladder. The use of a marker at the vaginal vault was allowed. However, the use a vaginal cylinder for the planning CT scan was discouraged since the insertion of a cylinder modifies the position of the vaginal vault. To allow for optimal contouring, the planning CT-scans had to be done with a slice thickness of at least 3 mm. To minimize the variability among volume definitions, consensus guidelines for the clinical target volume (CTV) were developed, posted on the RTOG website and published [27]. The contouring was done on the full bladder CT-Scan. Two CTVs were defined. The nodal CTV (nCTV) was defined as a volume covering the internal, external, presacral and low common iliac nodes and the perinodal tissue excluding adjacent bone, muscle and bowel. The vaginal CTV (vCTV) was defined as the upper half of the vagina and the parametrial tissue. The vCTV was also contoured on the empty bladder planning CT-scan. An internal target volume (ITV) was generated by the fusion of the vCTV of both the empty and full bladder planning CT scan. This strategy generated a margin for vaginal vault motion secondary to bladder filling. A planning target volume (PTV) margin of 7 mm was added to the nCTV and ITV. The following organs at risk (OAR) were also outlined bladder, rectum (from the anal junction to the sigmoid), femoral heads and bowel. The bowel was defined as the entire peritoneal cavity up to at least 2 cm above the PTV.

Patients were registered to receive pelvic IMRT to a dose of 50.4 Gy in 28 fractions to the PTV and concurrent weekly cisplatin at a dose of 40 mg/m^2 for a total of 5 cycles. The use of intracavitary high-dose rate (HDR) brachytherapy was left to the discretion of the treating

physician. When used, the prescription dose of brachytherapy was 6 Gy prescribed to the vaginal surface delivered for one or two fractions.

The dose constraints to the normal organs were the following: bowel < 30% to receive ≥ 40 Gy, rectum < 30% to receive ≥ 40 Gy, bladder < 35% to receive ≥ 45 Gy, femoral head < 15% to receive ≥ 30 Gy. Any IMRT treatment technique with the capacity to achieve these criteria was allowed.

Quality Assurance

The first plan for each institution had to be submitted for review prior to treatment. The plan was reviewed by both a physicist and one of the radiation oncology study chairs. Since the primary endpoint of this study was the reproducibility of the radiation technique, a central review was done for each patient enrolled in this trial to assess the dose coverage of the target volume and adherence to the dose constraints for the organs at risk. The dose coverage was scored as per protocol, variation acceptable (95-98 % of the PTV's being covered by 45.36 Gy or less than 5% of the PTV receiving a dose above 57.96 Gy) or deviation unacceptable (less than 95% of the PTV being covered by 45.36 Gy or more than 5% of PTV receiving more than 57.96 Gy).

Study chairs did not review cases from their own institution. The number of cases entered by the study chairs' institutions was capped to ensure that patients were enrolled from other institutions to truly test the transportability of pelvic IMRT to the multi-institutional setting.

Statistical Methods

All eligible patients starting radiotherapy were included in the analysis. The optimal two-stage design by Simon [29] was used. In this design, p represents the true probability that the final review is acceptable or marginally acceptable. A p close to 1 implies that the radiation therapy is reproducible in a multi-center setting. If p is ≤ 80%, the goal was to have at most a 5% probability of concluding that the technique is reproducible ($\alpha = 0.05$). On the other hand, if p is ≥ 95% of the desired level, the goal was to have at most a 10% probability of concluding that the technique is not reproducible ($\beta = 0.10$). With these specifications, 19 eligible patients were required in the first stage. If ≥ 3 of the 19 treatments were scored unacceptable, then early stopping would have been recommended to the study chair. Otherwise, the trial was to continue until a total of 42 eligible patients were accrued. If ≥ 5 of the 42 treatments were scored as deviation unacceptable, the technique would have been considered not reproducible, and a Phase III study would not have been pursued since this phase II study would have failed to establish the feasibility of transferring the use of pelvic IMRT in a multicentric clinical trial setting. Otherwise, the plan was to pursue the assessment of the value of this treatment regimen in a randomized Phase III study. Under the null hypothesis of an 80% reproducibility rate, this two-stage design had an expected sample size of 24.4. When p is 80%, this design minimizes the expected sample size among all designs satisfying the same specifications. To allow for an 8% ineligible/lost rate, the sample size for the cervical arm was 46 patients.

A secondary endpoint of this trial was to determine whether there was a reduction in grade ≥ 2 short-term treatment-related bowel AEs occurring within 90 days of treatment start as compared with standard treatment. For the purposes of this study, “bowel AEs” were defined as the following: diarrhea, enteritis, fistula, ileus, anal incontinence, GI necrosis, GI obstruction, GI perforation, GI proctitis and GI stricture/stenosis as graded by the National Cancer Institute

Common Terminology Criteria (CTC) for AEs version 3.0 (MedDRA version 6.0). Forty-two patients provided 64%, 88%, and 98% power to detect a reduction in short-term grade ≥ 2 bowel AEs (as defined above) from 40% to 25%, 20%, and 15%, respectively. This comparison was tested using a one-sided z-test of the difference of two proportions.

Other secondary endpoints presented in this report are those related to efficacy. OS is defined as death due to any cause. LRF is defined as any failure in the treatment field of the pelvis only. (PAF is defined as para-aortic nodal failure. DF is the appearance of distant metastases (which includes failure in the para-aortic nodes). Death, LRF, and DF are considered failures for DFS. All endpoints were measured from study entry to date of death/first failure. OS and DFS were estimated univariately with the Kaplan-Meier method [30] and LRF, PAF, and DF rates were estimated by the cumulative incidence method [31]. All analyses were performed using SAS/STAT® software.

RESULTS

Between March 2006 and October 2008, a total of 48 patients from 25 institutions were enrolled in this trial. Eight patients were excluded from all analyses, one did not receive any protocol treatment and seven were ineligible (two due to surgery, two due to laboratory work up, one due to chest CT-scan being outside of time frame, one due to positive margins, and one with undeterminable distant metastasis status). The analysis of the remaining 40 evaluable cervical cancer patients (eligible and who started protocol treatment) is the basis for this paper. Pretreatment characteristics are shown in Table 1. Most patients had FIGO stage IB disease (77.5%) and most were treated by a radical hysterectomy (70%).

Target Dose Coverage

The primary endpoint results of reproducibility based on adequate isodose coverage of the PTV are shown in Table 2. There were 40 evaluable cases for the primary endpoint, of which, none had a deviation unacceptable score for either the PTV vagina and/or the PTV nodal dose coverage. As the study was designed for 42 evaluable cases, under the worst case scenario, if it is assumed that the other two cases (inevaluable due to either being ineligible or not receiving protocol therapy) had a poor dose coverage score with an unacceptable deviation, then at most two cases would have isodose coverage scores of deviation unacceptable. Either way, the criteria of fewer than five cases deviation unacceptable for dose coverage of the PTVs is met. The excellent compliance rate is proof that pelvic IMRT in this protocol is reproducible in a multi-institutional setting.

As stated above, for each institution, the first case submitted was reviewed by one of the principal investigators prior to first treatment and if needed feedback was provided to adjust the volumes definition until adequate contouring was achieved. A total of 25 institutions enrolled cases in this trial, which means that 52% (25/48) of the cases submitted were reviewed prior to treatment initiation. All cases were eventually reviewed, and contouring and dose coverage were assessed.

Toxicity

Short-term treatment-related AEs are listed in Table 3. With respect to the protocol-specified secondary endpoint of reducing acute bowel-related GI AEs, there were seven patients

(17.5%) with grade 2 and two patients (5.0%) with grade 3 bowel AEs (eight diarrhea and one proctitis) and no patient developed grade 4 GI AEs. There was a statistically significant reduction in grade 2 or higher bowel AEs from 40% to 22.5% (one-sided p=0.043) when results from the intergroup collaborative study published by Peters et al (4) are compared to this study. There were no short-term treatment-related grade 5 AEs. Grade 3 and 4 non-hematologic AEs were reported for nine patients (22.5%) and one patient (2.5%), respectively. The rate of grade 3 and 4 worst overall toxicity was 42.5% (17 patients) grade 3 and 2.5% (1 patient) grade 4. All treatment-related AEs regardless of timing are shown in Supplemental Table 1.

Treatment Completion

The chemotherapy compliance observed on this protocol was excellent; 80% of patients were able to complete the chemotherapy treatment as per protocol. Details of the chemotherapy reviews are shown in Supplemental Table 2.

The median time to pelvic radiation completion was 38 days (min-max, 37-46 days).

Disease Control

Median follow-up at the time this analysis is 7.1 years (min-max: 0.6-9.5). After potential follow-up of over 10 years (data as of December 2016), 3 patients had LRF, 2 patients had PAF, and 4 patients had DF no PAF. The estimated five-year rates of LRF, PAF, and DF are 7.9% (95% confidence interval [CI]: 2.0%, 19.3%), 5.6% (95% CI: 1.0%, 16.6%) and 13.5%

(95% CI: 4.8%, 26.6%), respectively. The estimated five-year DFS and OS rates are 83.9% (95% CI: 67.6%, 92.4%) and 92.1% (95% CI: 77.4%, 97.4%), respectively (Table 4).

DISCUSSION

NRG Oncology/RTOG 0418 was the first collaborative group prospective study to establish the transportability of post-operative pelvic IMRT to a multi institutional setting. The primary endpoint of the study was met and it confirmed that when adequate quality control support is provided, the use of this treatment approach in a multi-institutional clinical trial is feasible.

There are many criteria which could be used to determine the transportability of IMRT to a multi-institutional setting, in this study adequate PTV coverage was selected as a surrogate. The success of this clinical trial can be attributed to multiple factors: the requirement for pelvic IMRT credentialing, establishing guidelines for contouring that allowed consistent delineation of target volumes and OAR, and real-time review of the first case from each institution prior to treatment.

This phase II study also showed that patients treated with pelvic IMRT in the adjuvant setting have statistically significantly less short-term bowel toxicity when compared to prior reported studies looking at a similar patient population. There were no grade 4 GI AEs in our cohort of patients while in the collaborative group study, 6 patients developed grade 4 GI AEs (four grade 4 diarrhea and two grade 4 small bowel obstruction). The investigators from RTOG 0418 were instructed to contour a bowel bag as opposed to individual bowel loops. In a setting where adaptive planning is not being done, choosing to protect the whole space where bowel

loops could be on any given day is probably the best strategy. An atlas of pelvic normal tissue contouring guidelines for conformal radiation therapy33 has been published and is a good guide for OAR contouring in the adjuvant setting for gynecological cancer patients.

The rate of local recurrence for patients with intermediate and high risk cervical cancer treated with adjuvant pelvic radiation or CRT varies between 10-14% at 4 years 2,3,4. The estimated rate of local recurrence at 5-year in this study is only 8%. The estimated overall 4-year survival in intermediate risk and high risk cervical cancer patients is 81%; the estimated 5-year overall survival in this series is 95%. These excellent results confirm that while IMRT allows for a reduction in GI toxicity when compared to historical data, this reduction in toxicity is not done at the cost of decreased disease control.

In the post-operative setting, the main challenge in PTV definition is to provide an adequate ITV margin on the vaginal vault. The strategy selected in this clinical trial was to acquire images with an empty and full bladder and to fuse the CTV vagina volume from both planning studies in order to generate an ITV. No measures were taken to account for the impact of the rectal filling on the movement of the vaginal vault. A careful review of the site of local recurrence for the patients enrolled in this clinical trial confirmed that this strategy was safe however moving forward an alternative to this approach would be to add an ITV margin of 1.5 to 2 cm to the vaginal vault tissue identified on the planning CT scan to account for various bladder and rectal filling.

Retrospective studies suggest that bone marrow sparing is another potential advantage of pelvic IMRT [34]. In this protocol, the bone marrow was not contoured as an organ at risk. Klopp et al analyzed the hematologic toxicity (HT) encountered on RTOG 0418 [35]. When compared to

historical data, patients in this trial were found to have a lower rate of HT. This might be part of the reason why the compliance rate to chemotherapy was very good.

Patients in this trial had an excellent rate of chemotherapy compliance, 80% of patients completed chemotherapy per protocol, and the median time for radiation completion was 38 days (min-max, 37 to 46 days) while it was 43 days (min-max, 35 to 79 days) in the CRT arm of the intergroup study [4]. Longer overall treatment time could potentially reduce biological effectiveness of radiation.

Patients with early stage high-risk cervical cancer enrolled to the Peters trial had a 10% rate of distant metastasis as the site of their first recurrence (either isolated 7%, or in association to a local relapse, 3%). The estimated 4-year survival of the combined modality arm on the Peters trial was 81%. To reduce this risk of metastatic disease and improve survival of this cohort of cervix cancer patients with high risk features identified at time of surgery, the potential benefit of adjuvant chemotherapy is now being studied in an intergroup clinical trial, NRG Oncology/RTOG 0724, a randomized phase III control study assessing the benefit of adding four cycles of carboplatin and paclitaxel to the CRT. If prolonged systemic treatment is proven to improve disease control for this patient population, protecting the bone marrow through the use of pelvic IMRT may become even more instrumental.

The safety of pelvic IMRT demonstrated in this study should not be considered transferable to the intact cervix setting. The changes in tumor volume observed in the radical setting add to the complexity of using IMRT with intact cervix. Until further investigations using high quality daily on-board imaging and adaptive treatment strategies are available, IMRT should be used cautiously for curative treatment of intact cervix.

In an era where there is increased consciousness about the importance of care value, the introduction of new technology should always be assessed in a randomized clinical trial (RCT). A RCT comparing IMRT to standard pelvic radiation was developed after NRG Oncology/ RTOG 0418. This RCT closed to accrual two years ago and results are currently under analysis for publication.

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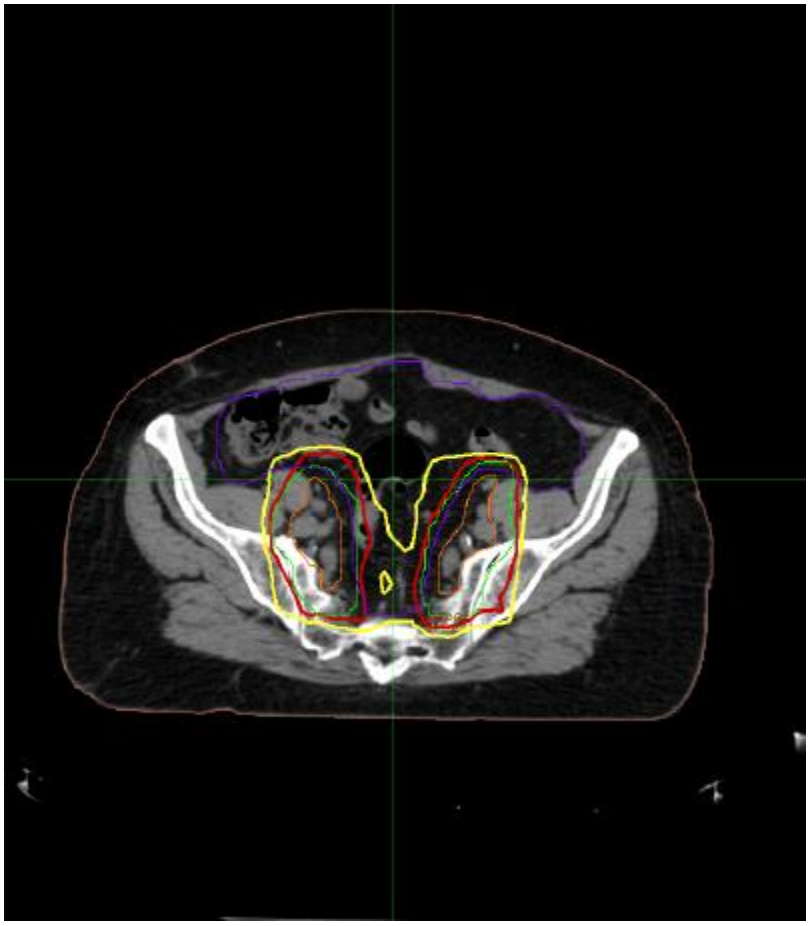
Figure 1-Axial RTOG0418



(Insert figures – one per page) (If applicable)

Insert Tables here (If applicable)

Insert Supplemental Materials (If applicable)