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Research on the Early Side Effects and Therapeutic Results of Extended Field-Intensity Modulated Radiation Therapy for Patients with Cervical Cancer who have Para-Aortic Nodal Metastases

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ABSTRACT
In cervical cancer patients with para-aortic lymph nodal metastasis, extended-field radiotherapy (EFRT) with concurrent chemotherapy is a standard treatment. EFRT with Intensity Modulated RT (IMRT) has been shown to lessen toxicities, yet the dose thresholds which minimize acute toxicity are unknown. The present study was undertaken to review early toxicity with EF-IMRT for carcinoma of the cervix in our patients and identify dose-volume parameters associated with ≥grade II hematological toxicity and diarrhoea. We conducted a retrospective analysis of consecutive cervical cancer patients treated with EF-IMRT for Para aortic lymph node metastasis. Patients were treated with rotational IMRT+/- NACT and/or concurrent chemotherapy (45-50 Gy/25#/5 weeks) and HDR-brachy therapy Varying doses to bowel and marrow were associated with acute hematological and gastrointestinal (diarrhoea and vomiting) toxicity. Receiver operator characteristics curves were used to derive thresholds predicting increased toxicity and tested on univariate and multi variate analysis. Finally, the disease free and overall survival (DFS and OS) were calculated. We included a total of 30 patients, the patients that received neo adjuvant chemotherapy (NACT) were 1/4 and the concurrent chemotherapy was 88%. In NACT and up front EF-IMRT, 22.6% and 9.7% of patients respectively experienced grade ≥III hematological (HT) and gastrointestinal (GI) toxicity (HT increase in patients receiving NACT [(≥grade III HT =67% (p=0.001)]. Higher ≥90% at 10 Gy in entire cohort bone marrow Volume receiving 10 Gy (V10>90%) was associated with development of ≥grade III HT (p=0.05). For GI toxicity, no dose volume thresholds could be validated. The median OS and DFS at 2 years was 56% and 54% respectively. EF-IMRT has acceptable grade III toxicity and is a viable treatment option for patients with cervical cancer who have para-aortic lymph nodal involvement. Future research must concentrate on reducing the toxicity of HT.

INTRODUCTION

Cervical cancer is the second most common cancer in women, worldwide, in the developing world. The standard of care is pelvic radiotherapy with concurrent cisplatin. Cervical cancer spreads methodically, first involving the lower pelvic lymph nodes and then involving higher pelvic and para-aortic lymph nodes[1]. Incidence of PALN disease has been reported by the Gynaecology Oncology Group to be 5% of stage I, 16% stage II and 25% stage III patients[1]. F-18-fluoro -2-deoxy-D-glucose (FDG)-positron emission tomography/computed tomography (PET/CT) appears to be more sensitive for detection of para-aortic lymph nodal than CT and abnormal FDG uptake has been detected in approximately 21% of patients with cervical carcinoma throughout all stage[2]. Para-aortic lymph nodal involvement is considered a negative prognostic factor, with a historical decreased overall survival in the long-term but selected patients may attain long-term survival after locoregional radiotherapy. Extended-field radiotherapy (EFRT) with concurrent chemotherapy currently represents standard recommendation however as optimal treatment for patients diagnosed with cervical cancer and who have para-aortic lymph nodal metastasis[3]. EFRT has been traditionally implemented through parallel opposed or conformal fields. EFRT may be performed using a conventional radiotherapy technique which results in the inclusion of large volumes of small bowel and bone marrow, consequently resulting in greatly increased gastrointestinal and hematological toxicity[4,5]. This toxicity is even aggravated by the addition of concurrent chemotherapy. With radiotherapy (hyper fractionated or standard) and combined chemotherapy, acute and late grade II or higher toxicity occurred in 83% and 41%, respectively. The use of hyper fractionation with conventional radiation portals was also associated with an extremely high rate of acute and late toxicities in the RTOG 9201 study[4,5]. IMRT allows greater conformity of the high dose volume for the prolonged targets and spare OAR, resulting in decreased acute and late toxicity. The literature is not entirely clear however on EFRT with IMRT may be associated with less acute and late gastrointestinal and marrow toxicities[3-5], but the dose thresholds for reduced gastrointestinal and marrow toxicities are not precisely defined. It has been suggested that both high and low dose effects on the bowel and marrow could be significant in the context of pelvic radiotherapy by which these effects on bowel and marrow are very evident in terms of subsequent hematological and bowel toxicities[6-8]. Image-guided, rotational intensity modulated radiotherapy has been used more for enhancing therapeutic gain by using ideal target coverage, nodal dose escalation and organ at risk dose reduction for extended-field intensity -modulated radiotherapy (EF-IMRT) in our institute. The aim of the current study was to report early toxicity with EF-IMRT for carcinoma of the cervix in our patient population and identify dose-volume parameters that predict ≥grade 2 hematological and diarrhoea.

MATERIALS AND METHODS

After institutional review board approval, all consecutive cervical cancer patients receiving EF-IMRT at our centre were included, irrespective of neo adjuvant and/or concurrent chemotherapy. All patients' case records were reviewed and patients' performance status, local stage, histology, the extent of nodal involvement and treatment were documented. An institutional guideline mandated that diagnosis of para-aortic lymph nodal has to be verified histologically or cytological for the performance of EFRT. In patients where a tissue diagnosis could not be attempted, a combination of clinical radiological criteria (para-aortic lymph nodal >10 mm in short axis in association with pelvic lymph nodes or positron emission tomography (PET), either uptake in pelvic lymph nodes or if PET shows positive uptake in both pelvis and para-aortic region) was considered as providing a diagnosis of para-aortic lymph nodal involvement. A multidisciplinary joint clinic decided on therapeutic management of these patients. Up front EFRT with concurrent chemotherapy (cisplatin 40 mg/m2) and brachytherapy was selected for patients with small nodes 3 cm node or nodal conglomerate or nodes above the renal hilum were planned to be treated with 2-4 cycles of neoadjuvant chemotherapy (paclitaxel 175 mg/m2 and carboplatin AUC 6) repeated every three weekly followed by imaging for response assessment. Next was EFRT in combination with chemotherapy and brachy therapy. CT-based simulation in supine position with knee rest was used for planning EF-IMRT. CT scans were performed from the tracheal bifurcation to mid-thigh after intravenous contrast with an interslice distance of 5 mm. The clinical target volume (CTV) was that of the entire gross tumour, plus cervix, uterus, parametrium and proximal half of the vagina (with the exception of cases with vaginal involvement, in which the whole vagina was included). Post-operative involving upper one-third of the vagina and bilateral parametrium was included. Planning target volume (PTV) for the primary was created by expanding this by 10 mm in the supero inferior and anteroposterior direction and 5 mm in media lateral direction. The lymph node clinical target volume (CTV) for para-aortic nodal region (superiorly from D12-L1 vertebral junction to the bilateral

common iliac, external/internal iliac, upper presacral (from S1-S2) and obturator regions) was included. Furthermore, for nodal simultaneous integrated or sequential boost, the grossly enlarged nodes (2 cm) were specified separately. For nodal boost, a different 5mm margin were generated to created CTV. Furthermore, nodal PTV was created with a 5 mm margin. Rotational IMRT was administered by either Tomotherapy or Volumetric Modulated Arc Therapy (VMAT). The PALN PTV, however, was treated to 45 Gy/25# and the pelvic PTV to 50 Gy/25#/5w. For nodal simultaneous integrated boost, the patients received 52.5-55 Gy/25# to gross nodes while for sequential boost, an additional 6-8 Gy/3-4 fractions. Boost was delivered sequentially or concurrently based on the decision of the treating physician. Contouring of organs at risk included: rectum, bladder, femoral heads, bowel bag, duodenum, kidneys and spinal cord. For all bones, bone marrow was defined retrospectively and included whole vertebral bodies from D10-L5, sacrum, coccyx, ilium, ischium, pubis, femoral heads and upper third of the femur. PTV coverage was ensured such that 95% PTV receives 95% prescription dose and all efforts were made to restrict mean dose to kidneys <12 Gy, Spinal cord maximum dose <45 Gy and Bladder V40 <75% and Rectum V40 <85%. With a lack of evidence-based dose volume constraints for bowel and bone marrow for EF-IMRT, all efforts were directed at reducing low dose spilling (V15 Gy for bowel bag) in the abdominal cavity. Dosage in the duodenum was critically assessed, especially in case of nodal SIB overlap. V55 Gy of the duodenum was <15 cc in all cases in which duodenal sparing could be accomplished. Bone marrow had no defined dose constraints. All patients utilized image guidance through cone beam CT. Patients then underwent HDR brachy therapy to a dose of 7Gy×3 fractions prescribed to point A after the completion of EF-IMRT and selected patients with disease beyond point A underwent combined intra cavitary and interstitial radiation. The maximum planning goal was to deliver 78-84 Gy to point A., all patients were evaluated weekly during the treatment for acute toxicity. For gastrointestinal (GI) toxicity, it was graded using RTOG scale[7] laboratory toxicities were based on CTCAE version 4.0[8]. For patients receiving concurrent chemotherapy, weekly blood investigations were performed. After the completion of treatment, the first follow up was at 6 weeks to evaluate acute toxicity and disease response. Follow up was done every 3 months for the first 2 years, 6 months for next 5 years and annually thereafter. Evaluation of nodal response at the first follow up was performed through a response CT imaging. Follow up thereafter included clinical evaluation and imaging and was at the discretion of treating physician. The main goal of this study was to assess acute toxicity (recorded until 90 days after the end of treatment) and its relationship with dose-volume data. Receiver operator characteristics (ROC) curve analysis was performed to determine the area under the curve for dose to bowel bag and marrow and acute grade $\geq$2 and $\geq$3 haematological and gastrointestinal toxicity (diarrhoea), respectively. The cut-off thresholds used for predicting toxicity were determined and selected for univariate analysis as they fitted best both in terms of high specificity and moderate to high sensitivity for prediction of toxicity. The impact of patient and treatment-related factors on acute GI and haematological toxicity was assessed. Disease free survival (DFS) and overall survival (OS) was reported from the date of registration of the patient in the institute and impacting factors on OS including age, stage, bulk of PA nodal disease, location of PA nodes, use of NACT and dose to point a were analyzed. DFS and OS were analyzed using Kaplan-Meir method with the aid of IBM SPSS Statistics for Windows (Version 21.0. Armonk, NY: IBM Corp.). Prognostic factors on outcomes were assessed using log-rank tests. Cox proportional Hazards was used for multi variate analysis Statistical significance was set at p value <0.05.

RESULTS AND DISCUSSIONS

In total, there were eligible subjects from 30 patients. EF-IMRT was used to treat all. All patients in this cohort were metastatic to the pelvis and para-aortic lymph nodal. The average size of the para-aortic lymph nodal was 1.5 cm and the majority of patients presented with more than one para-aortic lymph nodal. More than half of the nodes were below the renal hilum (90%). At presentation, none of the patients had non-regional lymph node involvement or distant metastasis. In 8/30 patients, NACT was given followed by EFRT+/- concurrent chemotherapy and in 22/30 patients EF-IMRT and concurrent chemotherapy. EF-IMRT was administered alone (n=5) due to toxicity following earlier NACT (n=1) and due to contraindications for concurrent chemotherapy (n=4). Out of the 30 patients, 22 received concurrent chemotherapy while all of them received up front EF-IMRT. Ninety-seven (89%) patients received at least four cycles of concurrent chemotherapy of these were n=19. The OTTs were 8 weeks (7-11 weeks) at the median. In 3 patients, OTT >10 weeks was due to interruption of treatment because of varicella infection, thrombotic episode and infective diarrhoea, respectively. Planned EF-IMRT was completed in all patients. Among the up front EF-IMRT cohort, grade III or higher hematological or gastrointestinal (vomiting or diarrhoea toxicity occurred in 22.6% and 9.7% of patients, respectively. Except for three patients, all other patients underwent brachy therapy. Three patients (one with distant

metastasis prior to brachy therapy and two with infective complications) could not be fit for brachy therapy. NACT followed by EF-IMRT with concurrent chemotherapy was administered to 8 patients. Median para-aortic lymph nodal size was 2 cm (±0.78) in this subset The majority (67%) of patients with NACT had >1 para-aortic lymph nodal. There was no relationship between the size of para-aortic lymph nodal and likelihood of NACT (p=0.157) and the decision of whether or not to give NACT was made at the discretion of the physician. The regimen utilized most was 3 weekly paclitaxel (175 mg/m2) and carboplatin (AUC6), median three cycles (range: 1-3). In para-aortic lymph nodal, all patients demonstrated at least partial response to NACT. Most patients developed ≥grade II neutropenia on NACT and one patient developed grade 4 neutropenia with inability of any further delivery of chemotherapy. This means that within the NACT cohort, at least 50% of the population as a whole had baseline grade II hematological toxicity prior to commencing the EFRT+concurrent chemotherapy. All patients in the cohort (7/8) continued to concurrent chemotherapy. Five out of eight patients had to be admitted with grade 3 diarrhoea and a break of treatment during radiotherapy. The mean treatment holiday was 6 days (4-11 range). During RT, 7 patients needed G-CSF support and 8 experienced blood transfusion. All patients had initiation of brachytherapy on time after EFRT and most of the break was found in external radiation. These results are statistically significant and, taken together, both suggest that grade III leucopenia, neutropenia, or any grade III hematological toxicity increases in patients receiving NACT prior to EF-IMRT or concurrent chemotherapy.

As per ROC analysis and existing data for pelvic radiation from INTERTECC protocol[9] a cut-off of 75% and 90% for V10 and 65% and 75% for V20 were assessed. V10 >90% characterized more commonly ≥grade 2 HT (85% vs. 35% p=0.05) and V10 >75% showed a trend towards increased anaemia (73 vs 44%., p=0.09). Excluded the patients with NACT, V10 >75% had much more ≥grade 2 anaemia (72% versus 16%., p=0.01) respectively. The ROC cut-off of V45 bowel bag was 300 cc and V40 bowel bag was 500cc for bowel toxicity. A cut-off neither influenced ≥grade 2 GI toxicity. SPACE FOR TABLE T15.3: V45 of 200 ccs, V40 of 250 ccs and V30 of 500 ccs all were not able to determine increase acute GI toxicity. As such, dose constraints for limiting acute gastrointestinal toxicity could not be agreed upon for the bowel. It should be noted, however, that none of the bone marrow constraints had been applied prospectively, but rather had been achieved through clinical planning of EF-IMRT in the routine application of this approach. Twenty-seven patients had a complete response at the site of the primary on first follow up post radiotherapy. This group included patients who underwent adjuvant postoperative RT. With (chemo)-radiotherapy, 50% of patients experienced a complete response at the para-aortic lymph nodal and 90% at least a partial response at PALN. The median follow for the cohort was 12 months (range: 3-32). The pelvic control rate was 93% and PALN control rate was 93% at last follow up. Most patients failed distally at multiple sites (lungs (n=3), media stinum (n=2), para-aortic region (n=2), supra clavicular fossa (n=2), peritoneum (n=1) and bones (n=1)). One patient was locally uncontrolled (without DM) and one patient failed at the treated para-aortic nodal field (without DM). The majority of patients with failure at para-aortic lymph nodal also had multiple other distant failure sites. At 2 years, OS and DFS was 56% and 54%, respectively. The 2-year OS and DFS were 89% and 67%, respectively, for NACT and EFRT and 51% and 51%, respectively, for up front EF IMRT.

EFRT and concurrent chemotherapy is the standard of care for cervical cancer patients with para-aortic lymph nodal involvement[9] and 2-year survival is 46-60% after this treatment[10]. Because distant metastasis in this cohort was high and systemic chemotherapy might be intensified. Nonetheless, the high rates of >grade III hemotoxicity and gastrointestinal toxicity (up to 80%) threaten patients and may compromise the possibility to tolerate this intensive therapeutic strategy, or to receive it in a timely fashion and produce excessive late toxicity and in consequence inferior outcome[10,11], for example, try to diminish acute toxicity by hyper fractionated RT[11], then combined with Amifostine to EFRT[10], leaving either exaggerated or similar toxicity without gain in results who had achieved this[12]. Recently, IMRT has been assessed for its potential ability to reduce acute toxicity by decreasing doses to bowel and bone marrow during EFRT. In other series, where postoperative extended field radiation is used or para-aortic radiation for positive common iliac nodes, survival with similar toxicity has been reported to be higher, combined external beam radiotherapy and brachytherapy with concurrent cisplatin has an OS of 36-65% with grade III/IV toxicity 10%-50% at 3 years. IMRT has been used since previous decade to make EF-IMRT more tolerable but the heterogeneous rates of toxicity seen amongst different series may represent a deficiency in protocols around bone marrow and GI sparing when extended fields are used. Though studies have been focused on identifying dose-volume limits for these organs in pelvic IMRT treatment, information is sparse regarding sound constraints for EF-IMRT in patients with cervical cancer. Since significantly more bowel and bone marrow are irradiated within the RT fields for these patients, there is a need to define dose

constraints specific to this sub population. Thus we performed the present study to establish the relationship of irradiated marrow and bowel volumes with the outcome in patients treated with EF-IMRT. Grade ≥III acute hematological toxicity occurred in 22.6% of the patients in our series and 9.7% in those treated with up front EF-IMRT and concurrent chemotherapy. These are comparable to the recently reported series with IMRT . Bone Marrow V10 >90% had a significant association with higher ≥grade 2 HT (p=0.04). Even excluding NACT patients, V10 >75% was significantly associated with higher ≥grade 2 anaemia indicating this may be a useful constraint identifier to prospectively apply to bone marrow to limit risk of hematological toxicity. A phase 2 trial is currently underway to explore the hypothesis that reducing pelvic bone marrow radiation dose will reduce hematologic toxicity and allow for improved chemotherapeutic delivery in patients receiving CRT.

CONCLUSION

The INTERTECC-2 randomised controlled trial is the first to test the hypothesis and found that, compared with CT based bone marrow sparing IMRT, PET IG-IMRT is superior in reducing HT rates, in keeping with previous modelling studies[6]. FLT PET is a potential novel imaging modality that has been previously reported in characterizing bone marrow activity and can offer this ability to address the challenge of targeting morphologically functional bone marrow. Though such thresholds have been established for pelvic RT in which there is a relationship between the volume of bowel irradiated and acute GI toxicity[12], we could not validate any of the bowel thresholds, i.e., volume irradiated by 15-40 Gy in the current analysis. We additionally tested dose constraints for the spine proposed in EMBRACE II study protocol, but these were not able to be validated. This may be due to differences in upper margin of irradiated volume (to/just below renal vein vs. D12/L1 junction) and the sparing technique used to delineate bowel bag. Setting bowel dose thresholds, accordingly, will be one of the potential work for this cohort[4]. Patients in NACT had a trend towards improved OS and DFS in our cohort, although this did not reach statistical significance and the role of systemic chemotherapy integration requires further investigation. EF-IMRT is a feasible treatment technique in cancer cervix patients with involvement of PALN at presentation and can be delivered with acceptable hematological and GI grade III toxicity. It may be possible to reduce hematological toxicity even more by limiting 10 Gy to between 75%-90% of the volume of bone marrow, but a dose response relationship for gastrointestinal toxicity including diarrhoea could not be shown. Future research should aim to better delineate approaches to reducing toxicity to enable implementation of systemic chemotherapy in high risk groups.

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