Feasibility and Safety of High Dose Chemoradiation in Locally Advanced Cervical Cancer: A Preliminary Experience of Gynecologic Oncology Management Italian Team

Donatella Russo[1,6], Graziana Ronzino[2,6], Antonella Papaleo[1,6], Elisa Cavalera[1], Angela Leone[1], Marianna Giampaglia[2,6], Simona Caretto[3,6], Fabrizio Totaro Aprile[4,6], Alex Cristiano De Marzi[5,6], Mario Santantonio[1,6], Antonio Perrone[4,6] and Andrea Tinelli[4,6,*]

[1]*Radiotherapy Unit - "Vito Fazzi" Hospital – Lecce, Italy*

[2]*Oncology Unit - "Vito Fazzi" Hospital - Lecce, Italy*

[3]*Gynecology and Obstetricy Unit - "I. Veris Delli Ponti" Hospital – Scorrano, Italy*

[4]*Gynecology and Obstetricy Unit - "Vito Fazzi" Hospital – Lecce, Italy*

[5]*Gynecology and Obstetricy Unit - "San Giuseppe da Copertino" Hospital – Copertino, Italy*

[6]*Disease Management Team of Gynecologic Oncology – Lecce, Italy*

Abstract: Locally advanced cervical cancer has a poor prognosis and is difficult to treat by surgery; authors' evaluated feasibility and safety of the simultaneous integrated boost (SIB) technique for dose escalation in patients with cervical cancer using a rotational dynamic Intensity Modulated Radiation Therapy Technique (VMAT®).

Authors evaluated 10 patients affected by loco-regionally advanced, node negative, inoperable cervical cancer. All women received primary chemoradiation (CRT). Six pts received three cycles of platinum-based chemotherapy (CT) plus CRT. Three Programmed Temperature Vaporization (PTV) were delineated: PTV1 (primary, cervix and parametria with a 1cm-margin); PTV2 (body of uterus with a 1cm-margin); PTV3 (pelvic nodes). PTV1 was defined using image fusion between CT-scan and RM or PET/CT. Treatment plans, calculated using a rotational dynamic Intensity Modulated Radiation Therapy (IMRT) system on Oncentra Masterplan® (VMAT®), and consisted in a simultaneous integrated boost. Total treatment time was 45 days. Concomitant CT consisted of weekly cisplatin 40 mg/m^2. Dose–volume histograms and acute gastrointestinal, genitourinary, and hematological toxicity were evaluated. Secondary endpoint was evaluation of short term disease free survival. Three months after CTRT, patients were revaluated with colposcopy and cytology and Pelvic imaging. After six and twelve months from CTRT, reevaluation included PET-CT or Chest CT scan and Abdominal and Pelvic RM. All patients concluded radiation without suspension. Cytology demonstrated complete response (CR) in 4 pts in the ERT fraction of brachytherapy (BRT) group and in 1 pts in ERT alone group. All other patients showed a partial response (PR) > 75%. After a median follow up of 20 month (range 16-22), 5 patients are free from disease (NED), 4 patients are alive with disease (AWD) and 1 patient died after three months (DOD). In 2 AWD patients, re-staging PET showed a RC of pelvic disease with evidence of disease in lomboaortic nodes. One of them received salvage radiation therapy on recurrence. After this preliminary experience, in patients with inaccessible cervical canal, authors could propose the dose escalation on PTV1, with the aim of delivering BED as near as possible to 85Gy.

Keywords: Advanced cervical cancer, chemoradiation, chemotherapy, brachytherapy, external radiotherapy, Intensity Modulated Radiation Therapy, Programmed Temperature Vaporization, Biological Effective Dose, Radiation Therapy Oncology Group, colposcopy, cytology, gynecological cancer, lomboaortic nodes, CT-scan, RM, and PET/CT.

INTRODUCTION

The Radiotherapy represents an important challenge in the management of locally advanced cervical cancer, when the radical surgery is not feasible. However, local recurrence rate is very high in locally advanced or node positive stages, reaching in some series 70% [1-3].

Guidelines suggest that doses of 85 Gy delivered to point A could be considered potentially curative in locally advanced cervical cancer [4]. In standard radiation treatments of cervical cancer, doses biologically equivalent to 85 Gy can be reached with a combination of conventional fractionated 3DCRT and hypofractionated brachytherapy. In node positive disease or in locally advanced cancer with stenosis of cervical canal, high external beam doses are necessary for local control of disease, but the proximity of healthy tissues as rectum, bladder and femoral heads can limit dose prescription. In fact, pelvic lymph node regions lie adjacent to the major pelvic organs such as small bowel, bladder and rectum and together with the pelvic floor form a cup-shaped volume, so most of the pelvis contents are exposed to the

*Address correspondence to this author at the Department of Obstetrics and Gynecology, Division of Experimental Endoscopic Surgery, Imaging, Technology and Minimally Invasive Therapy, Vito Fazzi Hospital, Pzza Muratore, 73100 Lecce, Italy; Tel: +39/339/2074078; Fax: +39/0832/661115; E-mail: andreatinelli@gmail.com

E-ISSN: 2309-6160/13

prescribed radiation dose [5]. This leads to increased acute and late toxicities. Grade III radiation cystitis and proctitis are in the range of 3–15% after radiation alone and, in combination with chemotherapy, toxicity can be expected to be still higher [6-7]. Acute toxicity, often causes interruption or discontinuance of radiation treatment, with consequent potential impact on the outcome, since literature data suggest that local control can be reduced by total treatment time longer than 8 weeks [8-11]. Intensity Modulated Radiation Therapy (IMRT) improves dosimetric results, limiting radiation delivered to normal tissue and allowing dose escalation to target volume, probably producing favourable clinical outcomes such as lower rates of gastrointestinal and urinary toxicity after whole pelvis irradiation [12-14]. Moreover, IMRT allows simultaneous integrated boost delivery, shortening treatment time when brachitherapy is not performable. In this paper, authors evaluated feasibility of dose escalation in locally advanced cervical cancer treatment using a rotational dynamic Intensity Modulated Radiation Therapy Technique (VMAT®). VMAT® delivers radiation by rotating linac gantry around the patient through one or more arcs with radiation continuously on. As it does so, a number of parameters can be varied, including MLC aperture shape, fluence output rate (dose rate), gantry rotation speed and multileaf collimator (MLC) orientation [15-16]. Treatment is performed by rotating the gantry over a single or dual arc(s), with MLC set and shaped to cover the target. This entails rapid execution of a sequence of control points each defining multileaf collimator (MLC) shape, MLC segment dose, and a gantry-angle window across which each shape sweeps dynamically. The aim of this paper is to describe a protocol that provides radiation delivery in a simultaneous integrated boost through the use of a volumetric IMRT technology. We evaluated early toxicity of high dose IMRT with concomitant chemotherapy in patients affected by locally advanced, inoperable cervical cancer. The secondary endpoint was evaluation of the short-term disease-free survival.

MATERIALS AND METHODS

Since May to December 2011, eighteen patients with histological confirmed cervical cancer were evaluated in our Disease Management Team for Gynecologic Malignancies. Because of locally advanced disease (stage IIB-IV), ten of them were not suitable for radical surgery.

In our institution, in patients with cervical cancer in stage > IIB chemoradiation (CRT) is indicated as definitive treatment [4], while patients with inoperable stage $\leq$ IIB receive neo-adjuvant chemotherapy with 3 cycles of Taxotere-Ifosfamide-Cisplatin (TIP) and re-staging to evaluate the eventual down-staging and consequent surgery indication. CRT has been indicated as definitive treatment in four patients, while six patients underwent induction chemotherapy followed by definitive chemoradiation, because the disease was still inoperable. To computerize a radiation treatment plan, in every patient a CT-scan in treatment position was obtained. Each patient was instructed to empty the rectum every day (even using a laxative in case of constipation) and to control bladder repletion by emptying it and drinking 1/2 litre of water 30 minutes before each radiotherapy procedure (CT scan and each treatment fraction). On each CT scan three clinical target volumes (CTV) were delineated: CTV1 including primary and involved nodes (GTV= gross tumor volume) with a 5 mm-margin, cervix and parametria, CTV2 includes body of uterus and CTV3 including pelvic nodes (obturator, internal and external iliac, common iliac and presacral nodes). In one patient with positive pelvic node lomboaortic prophylactic irradiation was performed. A CTV4 including lomboaortic nodes was defined in slice below a plan encompassing kidneys' hilum. GTV and CTV1 was defined using image fusion between CT-scan and RM or PET/CT. To obtain planned target volumes, an additional three-dimensional 5 mm-margin was added to CTVs. Treatment planning system was Oncentra Masterplan® and radiation therapy was delivered with VMAT®. In each treatment plan a simultaneous integrated boost (SIB) – i.e. the delivery of different doses to different volumes during the same radiation fraction- was calculated.

Before the treatment planning all the patients were evaluated through an hysterometry, In patients with accessible cervical canal, prescription doses were 60/2Gy to PTV1 and PTV2 and 54/1.8Gy to PTV3 and PTV4. Total treatment time was 45 days (Figure **1A**). At clinical evaluation, four patients presented cervical canal involvement and were judged not eligible for BRT. In these patients radiation doses were 69.9/2.33Gy to PTV1, 60/2Gy to PTV2 and 54/1.8Gy to PTV3 in 30 fractions. Total treatment time was 40 days (Figure **1B**). Each patient received concomitant chemotherapy, which consisted in six weekly administrations of cisplatin (40 mg/m$^{2)}$. Radiation toxicity prediction was performed on dose–volume histograms, using QUANTEC healthy tissue constraints [17-18]. The organs at risk of toxicity (OARs) were delineated according to the consensus guidelines

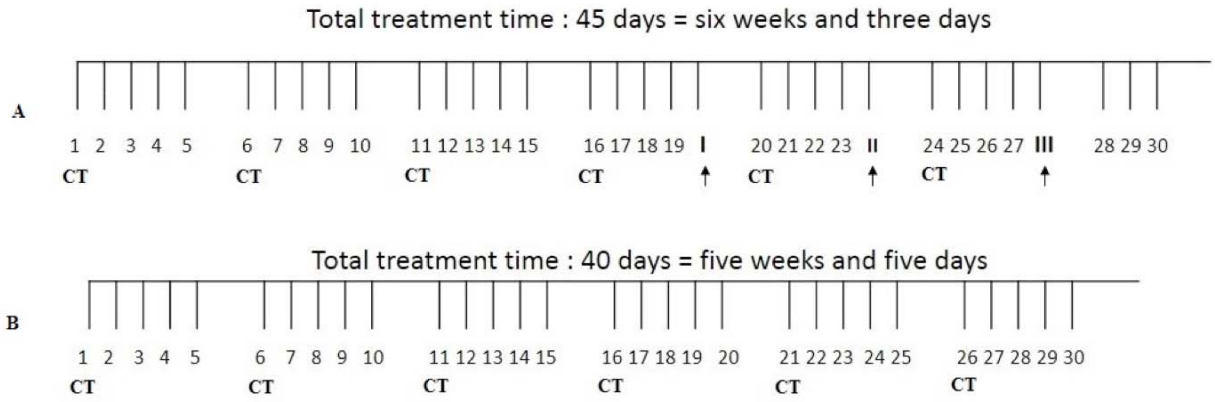

Figure 1: A: schedule with combination of external beam radiation (EBR) in arabic numbers, and brachitherapy (BRT) in roman numbers and arrows. **B**: schedule with external beam radiation alone. CT: chemotherapy administration.

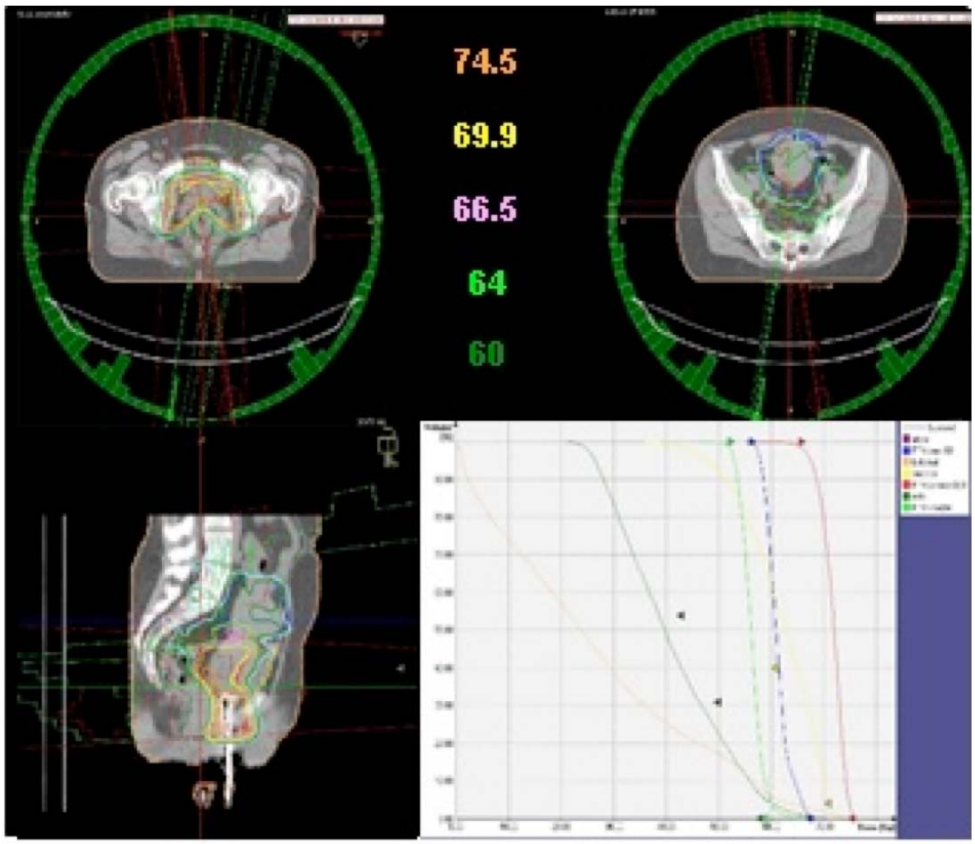

Figure 2: Example of treatment plan and dose volume histogram (DVH).

suggested by the Radiation Therapy Oncology Group (RTOG) [19]. An example of treatment plan and dose volume histogram (DVH) is shown in Figure **2**. Acute gastrointestinal and genitourinary side effects were evaluated during weekly examination and hematological toxicity was monitored with weekly blood cells count. Toxicity was classified according to RTOG Acute Radiation Morbidity Scoring Criteria. Disease re-staging was performed after three months from treatment completion. Each patient underwent colposcopy and cytology and pelvic imaging. Follow-up consisted in PET-CT or Chest CT scan and Abdominal and Pelvic RM after six and twelve months from CRT.

RESULTS

In any treatment plan, reporting of PTVs evaluated on DVHs was at least V95=95%. Dose constraints to OARs were respected. Toxicity pattern was represented by gastrointestinal side effects G1 in 5 patients and G2 in 3 patients; genitourinary side effects G1 in 4 patients and G2 in 2 patients. No G3-G4 events were registered during radiation or in the ninety days

after treatment conclusion. All patients complete radiotherapy without suspension. Only one patient with disease infiltrating bladder wall, after four months developed a fistula between bladder and vagina which required surgical correction. One patient developed G2 anemia, which needed Eritropoietin administration.

Biological Equivalent Doses were calculated according to linar-quadratic model formula:

$$BED = D(\alpha/\beta + d)/(\alpha/\beta + 2)$$

(D= total dose; d= dose fraction; α/β= parameter typical of each tissue, describing radio sensitivity of that tissue)

When combined ERT-BRT treatment was performed, BED on primary was 90 Gy, assuming a tumor α/β ratio of 10. In patients treated with hypofractionation, BED on primary was 72 Gy.

Re-staging after three months demonstrated complete response (CR) in four patients in the ERT-BRT group and in 1 pts in ERT alone group. All other patients showed a partial response (PR) > 75%. After a median follow up of 20 month (range 16-22), five patients are free from disease (NED), four patients are alive with disease (AWD) and one patient died after three months (DOD). In 2 patients AWD, re-staging PET showed a RC of pelvic disease with evidence of disease in the lomboaortic nodes. One of them received salvage radiation therapy on recurrence.

DISCUSSION

Generally, on patients with advanced cervical cancer and inaccessible cervical canal, literature suggests that, in the case of cervical cancer, curative Biological Effective Dose (BED) must be at least 85 Gy and this dose level is achievable when it is possible to combine ERT and BRT. Unfortunately, the increase of dose is limited by toxicity. The prescription of different doses to cervix and uterine body by SIB-IMRT could allow the dose escalation on primary, without toxicity arising, because of small bowel sparing. Moreover, IMRT, allowing banana-shaped isodoses, could provide to mantain rectum and bladder doses within tolerance. In all our patients, total treatment time was less than 8 weeks, as recommended by literature to improve local control.

In 2012, Cozzi *et al.* published a dosimetry comparison between conventional IMRT with fixed fields and volumetric arc modulated radiotherapy in cervical cancer. Authors concluded that volumetric modulation provides to better OARs sparing without compromising target coverage [20].

Most literature about IMRT in cervical cancer suggests that results in terms of toxicity are comparable with those obtained with conventional treatment [21]. Also in our series, despite higher doses prescribed, toxicity pattern remains similar to 3DCRT.

Disease control remains an important issue in these patients. In fact, despite improvements in the outcomes of single or combined modality treatment for achieving higher local control of cervical cancer, local recurrence or distant metastasis after initial (surgical or radiation) treatment remain a major therapeutic challenge. Literature reports a 10-20% recurrence rate after surgery or radical radiotherapy in early-stage cancer; this rate tends to increase with stage growing and reaches 70% in women with positive nodes disease [1,3,22-23].

Currently, chemotherapy is the main treatment modality in recurrent or metastatic disease, but its effectiveness is relative poor comparing to other gynecologic malignancies. Although Cisplatin has emerged to be the most active agent with higher response rate when it is administered alone [24] or in combination with other agents such as paclitaxel, vinorelbine, gemcitabine and topotecan [25], most of the responses are partial and effective only in the short terms.

In a retrospective review of more than 526 patients with invasive cervical cancer, the 31% of patients developed tumor recurrence, of which 58% recurred within 1 year and 76% within 2 years [26].

In gynecologic cancers, intensity-modulated radiotherapy (IMRT) has increased the potential for an improved outcome in cervical cancer in comparison with 3DCRT. Compared to conventional EBRT and 3DCRT, IMRT allows a highly conformal dose distribution around the target with a steep dose gradient outside the targets, thus sparing OARs and providing an opportunity for dose escalation, arising tumor control probability and maintaining side effects incidence within tolerated ranges.

Based on the theoretical benefits of IMRT mentioned above, it is yet to be determined whether it has an impact on the global outcome.

A study by Piver *et al*. reported a 5-year survival rate of only 9.6%, with death rates of 16.1% from

complications and 74.1% from cancer. The intestinal complication rate in patients who received 60 Gy of split-course irradiation in 8 weeks was 61.9% and only 10.0% in the patients who primarily received 44–50 Gy in 4.5–5 weeks [27].

The results of RTOG 92-10 showed that twice-daily fractionation of para-aortic nodes (PALN) irradiation combined with chemotherapy is highly toxic, resulting in an unacceptably high rate (17%, 5 of 29) of Grade 4 late toxicity. One patient died of acute complications of the therapy [28]. However, in comparison to PALN conventional radiation techniques, the use of PALN-IMRT is feasible because of significant sparing of the critical normal structures [29-30]. The radiation dose to the GTV was escalated from the conventional 45–60 Gy, whereas the PTV region received 45 Gy [31]. Eight patients in our study were treated with PALN-IMRT, with a median dose to PTV of 50 Gy. Of these, 3 patients developed grade 3 leucopenia and 1 patient developed grade 3 intestinal obstruction 10 months after the radiotherapy.

In our series, only one patient received PALN irradiation. Toxicity pattern in this patient was not increased, because of high conformal dose distribution around lomboaortic region, with a rapid dose fall-off out of the target. This dosimetry allows OARs sparing, also in case of very near healthy tissue, such as kidneys.

In several studies, the use of IMRT in patients with cervical cancer showed clinical benefits such as reduction in acute gastrointestinal and hematological toxicity. Mundt *et al.* in a retrospective study comparing IMRT and conventional EBRT in patients with gynecologic malignancies, demonstrated a Grade 2 acute gastro- intestinal toxicity of 60% vs. 91% (p=0.002), while Grade 3 toxicity did not develop in any of the patients. No or only infrequent anti diarrhea medications were needed (75% vs. 34%, p=0.001). Grade 2 genitourinary morbidity was reduced from 20% to 10% after administration of IMRT [30], and chronic GI toxicity was 11.1% vs. 50.0%, (p=0.001) [32].

In Roeske's analysis, the most significant factor that was correlated with acute GI toxicity was the volume of small bowel receiving the prescription dose of 45 Gy [33].

Another side effect relatively frequent in pelvic irradiation is represented by hematologic toxicity, due to irradiation of the pelvic bone, home of 40% of the total body bone marrow reserve. Moreover, the use of concurrent chemotherapy, which has become the gold standard in locally advanced cervical cancer, increases the likelihood of developing clinical myelotoxicity. IMRT allows hematological toxicity reduction, due to pelvic bone sparing. In fact, patients using intensity-modulated whole pelvic radiotherapy experienced lesser Grade 2 or greater WBC toxicity than conventional whole pelvic radiotherapy (31.2% vs. 60%, p=0.08) [34]. In our series, only one patient developed hematologic toxicity (anemia requiring eritropoietin administration). This side effect is probably due to concomitant chemoterapy, since doses to pelvic bones resulted fully lower than those tolerated.

Another important advantage in using volumetric beam modulation consists in shortening fraction delivery duration [20], arising patient comfort and reducing intrafraction movements, so reducing geographical missing risk. Average delivery time was found to be 12 minutes.

CONCLUSIONS

The aim of this preliminary study is to describe the feasibility of an IMRT protocol for dose-escalation in locally advanced cervical cancer treatment. Despite higher prescribed doses, toxicity pattern seems to be in line with literature reports. This is likely to be referred to the greater efficiency of volumetric IMRT in healthy tissue sparing, so allowing dose escalation.

Due to low patients number affecting results' significance and short follow-up time, the true incidence of acute and late toxicity may be underestimated. Results, however, seems encouraging, but an higher number of patients and long-term follow-up studies are needed to confirm these results.

DISCLOSURE OF INTEREST

Authors certify that there is no actual or potential conflict of interest in relation to this article and they reveal any financial interests or connections, direct or indirect or other situations that might raise the question of bias in the work reported or the conclusions, implications or opinions stated, including pertinent commercial or other sources of funding for the individual authors or for the associated departments or organizations, personal relationships or direct academic competition

REFERENCES

[1] Delgado G, Bundy B, Zaino R, Sevin BU, Creasman WT, Major F. Prospective surgical-pathological study of disease-free interval in patients with stage IB squamous cell

carcinoma of the cervix: a Gynecologic Oncology Group study. Gynecol Oncol 1990; 38: 352-57. http://dx.doi.org/10.1016/0090-8258(90)90072-S

[2] Burghardt E, Baltzer J, Tulusan AH, Haas J. Results of surgical treatment of 1028 cervical cancers studied with volumetry. Cancer 1992; 70: 648-55. http://dx.doi.org/10.1002/1097-0142(19910601)67:11<2776::AID-CNCR2820671111>3.0.CO;2-L

[3] Stehman FB, Bundy BN, DiSaia PJ, Keys HM, Larson JE, Fowler WC. Carcinoma of the cervix treated with radiation therapy. A multi-variate analysis of prognostic variables in the Gynecologic Oncology Group. Cancer 1991; 67: 2776-85.

[4] NCCN Practice Guidelines in Oncology Version 1-2013.

[5] Ahamad A, D'Souza W, Salehpour M, Iyer R, Tucker SL, Jhingran A, Eifel PJ. Intensity-modulated radiation therapy after hysterectomy: Comparison with conventional treatment and sensitivity of the normal-tissue- sparing effect to margin size. Int J Radiat Oncol Biol Phys 2005; 62: 1117-24. http://dx.doi.org/10.1016/j.ijrobp.2004.12.029

[6] Lukka H, Hirte H, Fyles A, Thomas G, Johnston M, Fung MF, Browman G. Concurrent cisplatin based chemotherapy plus radiotherapy for cervical cancer - a meta-analysis. Clin Oncol 2002; 14: 203-12. http://dx.doi.org/10.1053/clon.2002.0076

[7] Tharavichitkul E, Pinitpatcharalerd A, Lorvidhaya V, Kamnerdsupaphon P, Pukanhaphan N, Sukthomya V, *et al*. Impact of incomplete plan to treatment results of concurrent weekly cisplatin and radiotherapy in locally advanced cervical cancer. J Radiat Res 2011; 52: 9-14. http://dx.doi.org/10.1269/jrr.10021

[8] Withers HR, Taylor JM, Maciejewski B. The hazard of accelerated tumor clonogen repopulation during radiotherapy. Acta Oncol 1988; 27: 131-46. http://dx.doi.org/10.3109/02841868809090333

[9] Lanciano RM, Pajak TF, Martz K, Hanks GE. The influence of treatment time on outcome of the uterine cervix treated with radiation: a patterns-of-care study. Int J Radiat Oncol Biol Phys 1993; 25(3): 391-97. http://dx.doi.org/10.1016/0360-3016(93)90058-4

[10] Petereit DG, Sarkaria JN, Chappell R, Fowler JF, Hartmann TJ, Kinsella TJ, *et al*. The advers effect of treatment prolongation in cervical carcinoma. Int J Radiat Oncol Biol Phys 1995; 32(5): 1301-307. http://dx.doi.org/10.1016/0360-3016(94)00635-X

[11] Perez C, Grigsby PW, Castro-Vita H, Lockett MA. Carcinoma of uterine cervix. I. Impact of prolongation of overall treatment time and timing of brachytherapy on outcome of radiation therapy. Int J Radiat Oncol Biol Phys 1995; 32(5): 1275-88. http://dx.doi.org/10.1016/0360-3016(95)00220-S

[12] Guerrero M, Li XA, Ma L, Linder J, Deyoung C, Erickson B. Simultaneous integrated intensity-modulated radiotherapy boost for locally advanced gynecological cancer: Radiobiological and dosimetric considerations. Int J Radiat Oncol Biol Phys 2005; 62: 933-9. http://dx.doi.org/10.1016/j.ijrobp.2004.11.040

[13] Ahmed RS, Kim RY, Duan J, Meleth S, De Los Santos JF, Fiveash JB. IMRT dose escalation for positive para-aortic lymph nodes in patients with locally advanced cervical cancer while reducing dose to bone marrow and other organs at risk. Int J Radiat Oncol Biol Phys 2004; 60: 505-12. http://dx.doi.org/10.1016/j.ijrobp.2004.03.035

[14] Zhai D-Y, Yin Y, Gong G-Z, Liu TH, Chen JH, Ma CS, Lu J. RapidArc radiotherapy for whole pelvic lymph node in cervical cancer with 6 and 15 MV: a treatment planning comparison with fixed field IMRT. J Radiat Res 2013; 54: 166-73. http://dx.doi.org/10.1093/jrr/rrs066

[15] Steve Webb. VMAT its role in Radiotherapy. Medicalphysicsweb-Review; Winter 2009 (http://medicalphysicsweb.org/blog/MPWRwinter09_digitalPDF.pdf)

[16] Guckenberger M, Richter A, Krieger T, Wilbert J, Baier K, Flentje M. Is a single arc sufficient in volumetric-modulated arc therapy (VMAT) for complex-shaped target volumes? Radiot Oncol 2009; 93: 259-65. http://dx.doi.org/10.1016/j.radonc.2009.08.015

[17] Viswanathan AN, Yorke LD, Marks LB, Eifel PJ, Shipley WU. Radiation dose-volume effects of the urinary bladder. Int J Radiat Oncol Biol Phys 2010; 76 (3): S116-S122. http://dx.doi.org/10.1016/j.ijrobp.2009.02.090

[18] Michalsky JM, Gay H, Jackson A, Tucker SL, Deasy JO. Radiation dose-volume effects in Radiation-induced rectal injury. Int J Radiat Oncol Biol Phys 2010; 76 (3): S123-S129. http://dx.doi.org/10.1016/j.ijrobp.2009.03.078

[19] Gay HA, Barthold HJ, O'Meara E, Bosch WR, El Naqa I, Al-Lozi R, *et al*. Pelvic normal tissue contouring guidelines for radiation therapy: a Radiation Therapy Oncology Group Consensus Panel Atlas. Int J Radiat Oncol Biol Phys 2012; 83(3): 353-62. http://dx.doi.org/10.1016/j.ijrobp.2012.01.023

[20] Cozzi L, Dinshaw KA, Shrivastava SK, Mahantshetty U, Engineer R, Deshpande DD, *et al*. A treatment planning study comparing volumetric arc modulation with RapidArc and fixed field IMRT for cervix uteri radiotherapy. Radiot Oncol 2008; 89(2): 180-91. http://dx.doi.org/10.1016/j.radonc.2008.06.013

[21] Gandhi AK, Rath GK, Sharma DN. Early clinical outcomes of Intensity Modulated versus Conventional Pelvic radiation therapy for locally advanced carcinoma cervix: a prospective randomized study. Int J Radiat Oncol Biol Phys 2012; 84(35): S17-S18. http://dx.doi.org/10.1016/j.ijrobp.2012.07.050

[22] Burghardt E, Baltzer J, Tulusan AH, Haas J. Results of surgical treatment of 1028 cervical cancers studied with volumetry. Cancer 1992 70: 648-55. http://dx.doi.org/10.1002/1097-0142(19920801)70:3<648::AID-CNCR2820700318>3.0.CO;2-R

[23] Liu S-P, Huang X, Ke G-H, Huang X-W. 3D Radiation Therapy or Intensity-Modulated Radiotherapy for Recurrent and Metastatic Cervical Cancer: The Shanghai Cancer Hospital Experience. PLoS ONE 2012; 7(6): e40299.doi: 10.1371/journal.pone.00402

[24] Moore DH, Blessing JA, McQuellon RP, Thaler HT, Cella D, Benda J, *et al*. Phase III study of cisplatin with or without paclitaxel in stage IVB, recurrent, or persistent squamous cell carcinoma of the cervix: a gynecologic oncology group study. J Clin Oncol 2004; 22: 3113-19. http://dx.doi.org/10.1200/JCO.2004.04.170

[25] Monk BJ, Sill MW, McMeekin DS, Cohn DE, Ramondetta LM, Boardmen CH, *et al*. Phase III trial of four cisplatin-containing doublet combinations in stage IVB, recurrent, or persistent cervical carcinoma: a Gynecologic Oncology Group study. J Clin Oncol 2009; 27: 4649-55. http://dx.doi.org/10.1200/JCO.2009.21.8909

[26] Van Nagell JR, Rayburn W Jr, Donaldson ES, Hanson M, Gay EC, Yoneda J, *et al*. Therapeutic implications of patterns of recurrence in cancer of the uterine cervix. Cancer 1979; 44: 2354-61. http://dx.doi.org/10.1002/1097-0142(197912)44:6<2354::AID-CNCR2820440653>3.0.CO;2-J

[27] Piver MS, Barlow JJ, Krishnamsetty R. Five-year survival (with no evidence of disease) in patients with biopsy-confirmed aortic node metastasis from cervical carcinoma. Am J Obstet Gynecol 1981; 139: 575-78.

[28] Grigsby PW, Lu JD, Mutch DG, Kim RY, Eifel PJ. Twice-daily fractionation of external irradiation with brachytherapy and chemotherapy in carcinoma of the cervix with positive para-aortic lymph nodes: Phase II study of the Radiation Therapy

Oncology Group 92-10. Int J Radiat Oncol Biol Phys 1998; 41: 817-22. http://dx.doi.org/10.1016/S0360-3016(98)00132-1

[29] Portelance L, Chao KS, Grigsby PW, Bennet H, Low D. Intensity-modulated radiation therapy (IMRT) reduces small bowel, rectum, and bladder doses in patients with cervical cancer receiving pelvic and para-aortic irradiation. Int J Radiat Oncol Biol Phys 2001; 51: 261-66. http://dx.doi.org/10.1016/S0360-3016(01)01664-9

[30] Du XL, Sheng XG, Jiang T, Yu H, Yan YF, Gao R, *et al*. Intensity-modulated radiation therapy versus para-aortic field radiotherapy to treat para-aortic lymph node metastasis in cervical cancer: prospective study. Croat Med J 2010; 51: 229-36. http://dx.doi.org/10.3325/cmj.2010.51.229

[31] Ahmed RS, Kim RY, Duan J, Meleth S, De Los Santos JF, Fiveash JB. IMRT dose escalation for positive para-aortic lymph nodes in patients with locally advanced cervical cancer while reducing dose to bone marrow and other organs at risk. Int J Radiat Oncol Biol Phys 2004; 60: 505-12. http://dx.doi.org/10.1016/j.ijrobp.2004.03.035

[32] Mundt AJ, Mell LK, Roeske JC. Preliminary analysis of chronic gastrointestinal toxicity in gynecology patients treated with intensity-modulated whole pelvic radiation therapy. Int J Radiat Oncol Biol Phys 2003; 56: 1354-60. http://dx.doi.org/10.1016/S0360-3016(03)00325-0

[33] Roeske JC, Bonta D, Mell LK, Lujan AE, Mundt AJ. A dosimetric analysis of acute gastrointestinal toxicity in women receiving intensity-modulated whole-pelvic radiation therapy. Radiother Oncol 2003; 69: 201-207. http://dx.doi.org/10.1016/j.radonc.2003.05.001

[34] Brixey CJ, Roeske JC, Lujan AE, Yamada SD, Rotmensch J, Mundt AJ. Impact of intensity-modulated radiotherapy on acute hematologic toxicity in women with gynecologic malignancies. Int J Radiat Oncol Biol Phys 2002; 54: 1388-96. http://dx.doi.org/10.1016/S0360-3016(02)03801-4

Received on 19-05-2013 Accepted on 21-06-2013 Published on 21-08-2013

DOI: http://dx.doi.org/10.12974/2309-6160.2013.01.01.2