Original Article

Comparative Study of Treatment Response and Toxicity of Four Field Box Technique Versus Two Field Technique External Beam Radiotherapy in Locally Advanced Carcinoma Cervix

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ABSTRACT

Introducation: External beam radiotherapy plays a pivotal role in locally advanced carcinoma cervix. EBRT treats the whole pelvis including the primary tumor along with the regional lymph nodes. Conventionally, EBRT planning is based on standard bony landmarks using X-rays and can be delivered by anterior–posterior and posterior–anterior (AP-PA) parallel opposed fields or the four field box technique. AP-PA field technique provides good coverage to the target volume. Four field box technique with parallel opposed AP-PA fields and two lateral opposed fields although has better dose distribution and decrease normal tissue toxicity, is time consuming. EBRT by AP-PA two field technique is generally used in our center due to less manpower and resources and huge load of patients. But, pelvic radiotherapy by 4 field portals has been proven by the trials that it has better tumor response. So, the objective of this study was to compare the tumor response and acute hematological and non- hematological toxicities between the two techniques.

Methods: One hundred and twenty patients with diagnosis of carcinoma cervix were enrolled in this study, sixty assigned in each group. Group A received radiation by AP-PA two field technique and Group B by 4 field box technique. Chemotherapy regimen was the same for the two groups. Treatment response and toxicities were evaluated after the completion of treatment and compared between two groups.

Results: All enrolled patients received planned treatment. The total duration of treatment in both the groups was 23 days. Loco-regional control with complete remission was 63.3 % in group A Vs. 73.3% in group B (p= 0.405). Acute toxicities of grade 1 and grade 2 were seen more in group A compared to group B, nausea (63.3% vs. 56.7% p=0.141), vomiting (13.3% vs. 20% p=0.234), diarrhea (10% vs. 6.7%), radiation dermatitis (3.3% vs. 0%). Hematological toxicities like anemia, thrombocytopenia and leucopenia were observed more ingroup A than group B.

Conclusion: Both two and four field box techniques are equally effective and feasible as statistically insignificant difference in the response rate and acute toxicities was observed in the two groups.

Keywords: External Beam Radiotherapy, concurrent chemotherapy, locally advanced cervical cancer

Introduction

Cervical cancer is the third most commonly diagnosed cancer in women with an estimated 529,800 new cases worldwide, more than 85% of which are in developing countries.[1] Globally, cervical cancer is the second most common cause of cancer-related mortality causing approximately 234,000 deaths annually among developing countries killing 40,000 women in developed nations.[2] With an incidence rate of 32.4 per 100,000 per annum[3], cervical cancer remains to be the leading cancer and cause of cancer

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deaths among females in Nepal, accounting to 21% of all female cancer.[3] The discrepancy in cervical carcinoma related mortality between developing and developed countries is a direct result of poor medical surveillance.

As there are less facilities of cervical screening in Nepal most patient of cervical carcinoma are diagnosed at advanced stage. Fortunately, patients diagnosed at an early stage are treated with surgery or radiotherapy which is often curative. Locally advanced cervical carcinoma is not amenable for surgery making radiotherapy the sole definitive treatment. Patients with locally advanced disease are at high risk for recurrence and account for most of the cervical cancer deaths.[4]

The management of advanced stage carcinoma of cervix with primary radiotherapy involves a combination of external beam radiotherapy (EBRT) plus either low dose rate (LDR) or high dose rate (HDR) intra cavitary irradiation. The goal of the treatment is to balance these two elements in a way that optimizes the ratio of tumor control to treatment complications. EBRT gives a homogenous dose distribution and treats the primary tumor and regional lymph nodes.[4] Conventionally EBRT planning is based on standard bony landmarks using X-rays, which can be delivered by using either a two field technique (anterior and posterior) or a four field box technique.[5-7] AP-PA field technique provides good coverage to the target volume whereas four field box technique with parallel opposed AP-PA fields and two lateral opposed fields has better dose distribution leading to decrease normal tissue toxicity.[8]

The most common technique for whole pelvic irradiation for cancer of the uterine cervix has been the AP-PA two-field technique. However, the four-field box technique has gained increasing acceptance. The advantage of four-field box technique is the use of lateral ports that spare the small bowel anteriorly and a portion of the rectum posteriorly from radiation. Radiographic and anatomic guidelines for AP/PA pelvic ports have been well established. However, guidelines for the lateral pelvic ports are poorly defined.[9] A review of literature shows great variability especially with regard to the posterior border.[10-12] With the use of sectional imaging, wide variations such as different levels of aortic bifurcation, altered sacral curvature, and varying course of pelvic vessels have been reported in the pelvic anatomy of individual patients as well.[13-15] This has led to development of modern techniques such as 3 dimensional conformal radiotherapy and intensity-modulated radiotherapy. These newer techniques have reported decrease in normal tissue toxicity, along with decrease in the chances of geographic miss. These are now being widely used in developed countries. Many centers of developing countries such as ours, where patient load is high, still prefer to use conventional X-ray-based planning using the standard bony landmarks. This is because x-ray-based planning is simple, less time consuming, and cost-effective.[8]

The aim of this study was to evaluate and compare between the two conventional techniques in terms of treatment response and toxicity.

Methods

Study settings: This is a hospital based analytical, prospective study undertaken in 60 patients with cervical carcinoma attending OPD at two cancer centers in Nepal, Clinical Oncology Department of Bir Hospital and Department of Radiation Oncology, B.P Koirala Memorial Cancer Hospital, Bharatpur.

Sampling techniques: This study included all female patients presenting in OPD diagnosed as cervical carcinoma. Patient written consents were taken and confidentiality was maintained.

Inclusion Criteria included:

1. Signed informed consent prior to enrollment.
2. Age >25 years
3. Eastern cooperative oncology group performance status 0-2
4. Histologically confirmed squamous cell carcinoma, adenosquamous, adenocarcinoma of cervix
5. Tumor classified as FIGO staging IIB to IVA

Exclusion Criteria included:

1. Eastern cooperative oncology group performance status 3-4
2. Patient not giving informed consent.
3. Patient received chemotherapy and radiotherapy prior
4. Patient diagnosed with other synchronous carcinoma
5. Creatinine clearance <40 ml/min

Those patients to be enrolled in the study were subjected to clinical physical examination, cystoscopy, histopathological and laboratory examination to confirm diagnosis. Clinical examination included

performance status, proper general examination, systemic examination and per vaginal / per rectal speculum examination. Radiological examination included x ray chest and USG abdomen and pelvis. All patients fulfilling the inclusion criteria were allowed to select random numbers from 1-60 during their OPD visits and randomized into two groups of odd and even numbers. The patients who selected odd numbers were allocated as Group A and received EBRT by AP-PA two field technique. The patients who selected even numbers were allocated as Group B and received EBRT by four field box technique.

Chemotherapy: All enrolled patients of cervical carcinoma were subjected to receive concurrent chemo-radiation as per 2 field technique and 4 field technique along with Cisplatin chemotherapy. Cisplatin was administered at a fixed dose of 40 mg/ m^2per weekly cycle for all patients with external beam irradiation.

Radiotherapy: Radiation was given by 6 MV Photon. Total dose of radiation was up to 46 Gy in 23 fractions in both arms. Radiation was given by opposed parallel anterior /posterior and four fields anterior/posterior, right and left lateral portals. It was given from Sunday to Thursday for four and a half weeks.

The standardized fields for anterior posterior AP-PA two field technique includes anterior and posterior incorporated superior border at L4-L5 space, an inferior border placed at lower obturator foramina or at least 3cm below the extent of clinically appreciated cervical or vaginal disease and lateral borders were placed 2 cm beyond the bony margins of the true pelvis. The portals for four field box technique includes the anterior and posterior portal same as two field technique. Lateral fields were placed with an anterior border anterior to symphysis pubis; posterior border to cover whole of the sacrum hollow.

All patients were kept in close observation during radiotherapy period for early identification of any toxicity. Grade I and II toxicities was carefully watched and managed accordingly. Patient who had grade I and grade II nausea and vomiting were managed with oral antiemetics. Patients with grade I and grade II diarrhea were also managed with anti-diarrheal. Blood investigations including total count, differential count, platelets, hemoglobin and renal function test were done every week during radiotherapy so that any deviation from normal blood parameter could be identified and corrected promptly. This helped to prevent unnecessary delay in radiotherapy. Patients who had encountered low hemoglobin < 10 g/dl during any week of treatment was transfused blood products before resuming the radiation therapy. Patient who had encountered low total counts with neutropenia was kept on hold of treatment. Patient with febrile neutropenia was admitted for intravenous antibiotics and was discharged after marrow recovery and was afebrile. The radiation therapy was resumed only after the absolute neutrophil count was more than 1500/ mm^3. After completion of treatment also patients were kept in close follow up for timely identification of other complications.

After completion of treatment, response was assessed clinically by per vaginal/speculum and per/rectal examination. Treatment response was assessed in both groups. Then, patients were kept in 3 monthly follow up and in each follow up clinical examination, blood investigation were done.

Statistical methods: Statistical analysis was also done using SPSS software after entering the data on a master chart. Results were taken out using independent t-test and chi-square test. Then the results were presented in tables, graphs and diagrams.

Results

A total of 60 patients; 30 patients in each group were included in study with the age ranging from 30 years to 75 years. The mean age of the study population was 52 years with a standard deviation of 8.59 in group A. Similarly, the mean age of the study population was 51.93 years with a standard deviation of 9.53 in group B.

Cases of cervical cancer of stage IIB – IVA were included. Among all the stage, there was more number of stage IIB patients in both groups (Figure 1).

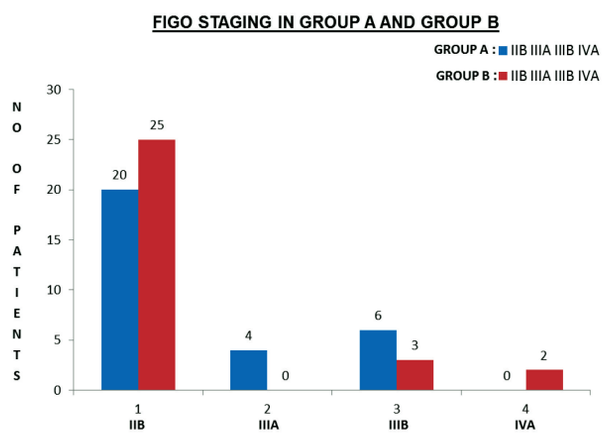

Figure 1: Stage wise distribution of participants in Group A and Group B

While observing the occurrence of anemia in both the groups, it was observed that anemia was more in Group A compared to Group B. During the 1st, 2nd, 4th, 5th week and 3 months anemia was observed more in Group A. Anemia in group B was seen in 3rd week only. In both Group A and Group B there was more grade1 anemia. Decreased hemoglobin was accounted mostly in the 5th week of EBRT (Figure 2).

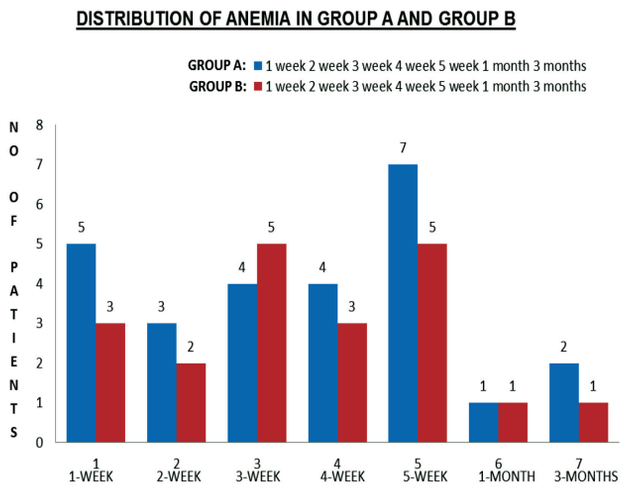

Figure 2: Comparison of anemia between Group A and Group B

While observing the occurrence of thrombocytopenia, it was seen in group A in all the weeks compared to group B. In both Group A and Group B there were grade 1 thrombocytopenia compared to grade 2 and grade 3. It was observed that leucopenia was in 1st week only in Group A whereas in group B it was observed in 2nd, 3rd, 5th weeks and1 month. In both the Group A and Group B there was grade 1 neutropenia compared to grade 2 and grade 3 (Figure 3).

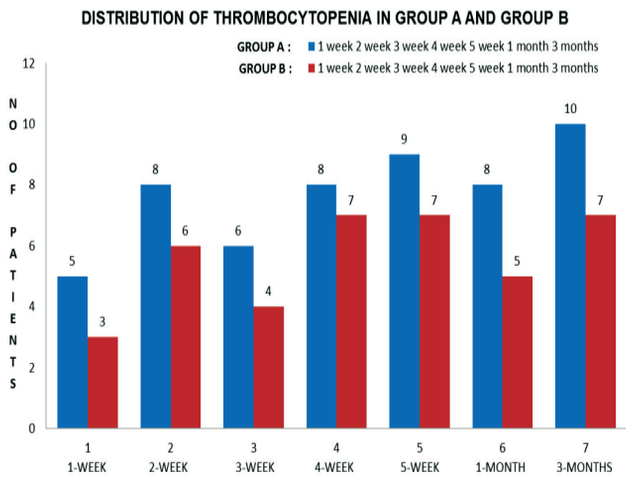

Figure 3: Comparison of thrombocytopenia between Group A and Group B

Decreased leucocyte count was accounted in group A compared to group B. Decreased leucocyte count was accounted in every week of treatment, mostly observed in 5th week of the treatment (Figure 4). In our study, both the groups received cisplatin chemotherapy of 40mg/m^2 which was given weekly along with radiotherapy. It was observed that nausea was more common in group A compared to group B but it was not statistically significant (p= 0.141). Vomiting was more common in group B compared to group A but it was not statistically significant.

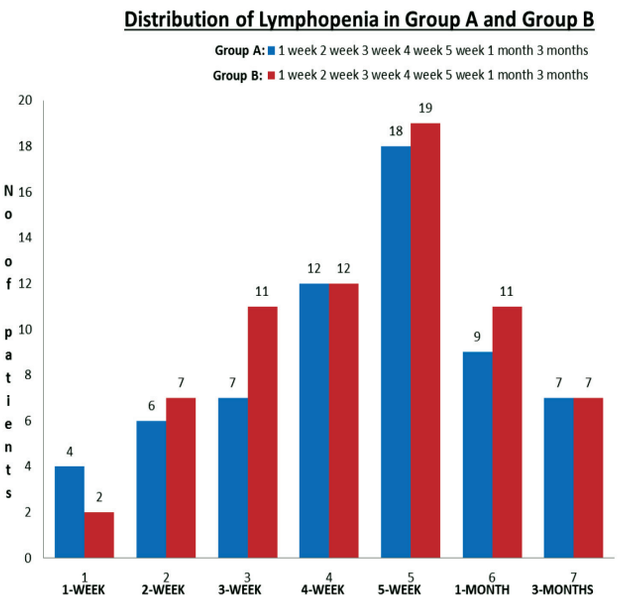

Figure 4: Comparison of Leucopenia between Group A and Group B

Complete remission was compared between group A and group B. Radiation by four field box technique resulted in better complete remission compared with AP-PA two field techniques but that was not statistically significant. Complete remission was in 73.3% in group B and 63.3% in group A. Complete response received in both the groups was 68.3%. Partial remission was more in group A compared to group B but not statistically significant. Partial response was 36.7% % in group A and 26.7 % in group B. Nausea was more common in group A compared to group B, but it was not statistically significant. (p= 0.141). Vomiting was more common in group B compared to group Abut it was not statistically significant. Diarrhea was more common in group A compared to group B, but it was not statistically significant. Radiation dermatitis was very rare and was seen in group A (Table 1).

Table 1: Comparison of treatment response and toxicity between Group A and Group B

Characteristics	Categories	Group A 2 Field n (%)	Group B 4 Field n (%)	Total	p-value
Response	Complete response	19 (63.3)	22 (73.3)	41 (68.3)	0.405
	Partial response	11 (36.7)	8 (26.7)	19 (31.4)	
	Absent	8 (26.7)	13 (43.3)	21 (35.0)	
Nausea	Grade 1	19 (63.3)	17 (56.7)	36 (60.0)	0.141
	Grade 2	3 (10.0)	0 (0.0)	3 (5.0)	
	Absent	23 (76.7)	24 (80)	47 (78.3)	
Vomiting	Grade 1	4 (13.3)	6 (20)	10 (16.7)	0.234
	Grade 2	3 (10.0)	0 (0.0)	3(5.0)	
	Absent	23 (76.7)	28 (93.3)	51 (85.0)	
Diarrhea	Grade1	3 (10.0)	2 (6.7)	5 (8.3)	0.12
	Grade 2	4 (13.3)	0 (0.0)	4 (6.7)	
Radiation dermatitis	Absent	29 (96.7)	30 (100)	59 (98.3)	1.00
	Grade1	1 (3.3)	0 (0.0)	1(1.7)	
Total		**30 (100)**	**30 (100)**	**60 (100)**	**-**

Discussion

Present study was carried out on histopathological proven cancer cervix patients to assess the treatment outcome and toxicities receiving pelvic radiotherapy by two field and four field technique. In this study patients have been divided in two arms receiving radiation by two field technique and four field box technique as in reference studies done by Gupta et al[4] and Yamazaki et al.[16] Enrolled patients in this study were of 30-75 years of age similar to the study conducted by Gulia et al.[8] As in the study of Gupta et al the patients enrolled in our study were all squamous cell carcinoma histology.[4]

The difference in the response achieved in the two groups was not found to be statistically significant. On analyzing our result for the response, we found 63.3% complete response in group A and 73.3% in group B. Gupta et al analyzed his study with complete response of 87.8% in group A and 85.75% in group B.[4] In a Japanese study conducted by Yamazaki et al no statistical difference was found on survival, relapse free survival and pelvic control rates between the two field and four field box technique.[17]

Kimet et al. concluded that pelvic control was 100% for Stage IB disease and 88% for Stage IIB disease and 50% for Stage IIIB disease.[9] In the pattern of care studies conducted by Caio et al. reported that a survival of 67.5% and pelvic control rate of 78.5% in the patients treated with EBRT.[24] Another study conducted by Kim et al[18] reported pelvic failure was 30.11 % for stage IIB, 52.31 % fir stage III B, and 69.2% for stage IV A, respectively. In a study conducted by Perez et al, the tumor-free 5-year survival rate was 68% in 276 patients with stage IIB, 45% in 237 stage III and one survivor in 18 stage IV patients.[10] The overall incidence of pelvic recurrences was 14% in stages IIB and 37% in stage III.

Yamazaki et al showed no statistical difference in survival, relapse-free survival or pelvic control rate between the AP-PA two-field and irregularly shaped four-field box technique groups.[16] The study concluded that without the CT simulation, four field technique had a geographical miss in including the primary tumor and concluded that AP-PA two field technique was as effective as Four field technique when it done without CT simulation. A study which was conducted by Kim et al showed that there was high local failure in patients with treated by four-field box technique pelvic radiation therapy with inadequate margin.[9] The study suggested that CT-treatment planning was recommended during four field technique. The most common sites of inadequate margin (<1.0 cm) from the conventional lateral pelvic portals was at the posterior margin and the rectal block. Another study conducted by Nagar et al that there was a potential

for geographic miss of the gross disease when conventional 4-field pelvic portals was used to treat cancer cervix without the aid of CECT defined tumor volumes.[16] The study had concluded that without the knowledge of precise tumor volume, the 4-field technique with standard portals was potentially risky as it may under dose the tumor through lateral portals and the standard AP-PA two field technique was a safer option. In a study conducted by Gulia et al, 48 out of 50 patients, the conventional four field box had failed to encompass the target volume.[8] The areas of miss were at the superior and lateral borders of the anterior-posterior fields, and the anterior border of the lateral fields. In our study the CT simulation for four field box technique was not feasible due to financial status. As per literature quoted above, the planning of four field without CT simulation leads to incomplete tumor coverage making AP-PA two field technique a safer option.

A study conducted by Pearcey et al to evaluate the toxicity and efficacy of concurrent cisplatin and radiation therapy by four field box technique in the treatment of patients with locally advanced squamous cell carcinoma of cervix showed that the treatment was well tolerated with all patients completing radiotherapy and there was only one case of grade 4 bowel toxicity.[19] A study was conducted by Tseng et al comparing concurrent chemoradiotherapy versus radiotherapy by four field box technique in advanced carcinoma of the uterine cervix showed that treatment-related toxicity appeared to be higher with the combination of radiotherapy and chemotherapy compared with radiotherapy alone (36.7% versus 17.7%, p =0.02).[20]

King et al also had evaluated the acute side-effects after concurrent chemo-radiation for carcinoma cervix.[21] This study concluded that weekly cisplatin-based chemoradiotherapy could be given with acceptable acute toxicity and excellent early control rates. At a median follow-up of 35 months: gastrointestinal (n = 57; 72%), (diarrhea in 51 women and nausea and vomiting in 12 women), hematological (n = 55; 70%), infections (n = 27; 34%) and skin reactions (n = 27; 34%). 28 women developed grade 1 or 2 anemia, 7 women developed grade 1 or 2 neutropenia and 2 women experienced grade 3 or 4 thrombocytopenia was noted. EBRT by four field technique and concurrent cisplatin in locally advanced cervical cancer was a study conducted by Kadkhodayan et al.[22] Nausea and vomiting was observed which was of grade I (3.3%) and II (10%) and diarrhea of grade I (6.6%), grade II (3.3%), grade III (6.6%) and grade IV (6.6%). Hematological toxicity was also observed among which anemia was of grade I (33.3%), grade II (23.3%). Neutropenia have been recorded among which grade I (30%) grade II (33.3%), grade III (13.3%). Oikeet et al. compared the incidence and degree of hematological toxicities between innovator and generic cisplatin formulation.[23] The number of patients showing Grade 1, 2, 3 and 4 leukopenia were 1(4.5%) ,14 (64%) , 7(32%) , 0 (0.0%) in the innovator group and 1(4.5%) , 6 (27%) , 13(59%) , and 2(09%) in the generic group respectively. The number of patients showing grade 3-4 leukopenia was significantly in generic group than in innovator group (p=0.034). There was no significant difference in incidence and degree of thrombocytopenia in two groups.

In summary, our study demonstrates that the cervical cancer patients can be considered for two field pelvic radiotherapy in terms of treatment response and toxicity.

Conclusion

After analyzing the results, the local control rate with immediate complete remission was observed in 4 field box technique than 2 field technique and the treatment toxicities were also observed to be more on 2 field technique. However, the results were not statistically significant. So, in a center like ours with less manpower and infrastructure, pelvic radiotherapy by 2 field technique can also be recommended. Further studies and trial need to be done to confirm the better response to 4 field technique.

External beam radiation therapy can be still be practiced by Two Field technique in locally advanced carcinoma cervix when compared to four field box technique. The advantage of this technique is that it is less time consuming, more number of patients can be treated.

References

1. Ferlay J, Shin HR, Bray F, et al. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer, 127, 2893-917; 2008.
2. Bradley J. Monk, Krishnansu S. Tewari, Wui-Jin Koh et al. Multimodality Therapy for Locally Advanced Cervical Carcinoma: State of the Art and Future Directions. J Clin Oncol 25:2952-2965;2007.
3. Pradhananga KK, Baral M, Shrestha BM et al. Multi-institution hospital-based cancer incidence data for Nepal: an initial report. Asian Pac J Cancer Prev, 10, 259-62; 2009.
4. Deepak Gupta, Pragya Shukla, Shyam Singh Bist

et al.Comparitive study of efficacy, tolerability of four field box technique Vs. Two field anterior posterior technique in locally advanced carcinoma cervix. Cancer Biology and Therapy8:9,759-764; 1 May 2009.

5. Marcial VA, Marcial LU. Radiation therapy of cervical cancer—new developments.Cancer Suppl 71:1438-45; 1993.
6. Fletcher GH, Hamberger AD. Female pelvis: squamous cell carcinoma of the uterinecervix. In: Fletcher GJ, ed Textbook of radiotherapy, 3rd ed. Philadelphia. PA: Lea andFebige 720-73; 1980.
7. Perez CA. Carcinoma of the uterine cervix. In: Brady LW, Perez CA, 2nd ed. Principlesand practice of radiation oncology. Philadelphia: Lippincott Co 1992 1143-202; 1992.
8. Abhishek Gulia, Firuza Patel, Bhavana Rai et al.Conventional four field radiotherapy versus computed tomography-based treatment planning in cancer cervix: A dosimetric study.South Asian J Cancer. Jul-Sep; 2(3): 132–135; 2013.
9. Robert Y. Kim, M.D., L. Scott Mcginnis, M.D., Sharon A. Spencer, M.D. et al.Conventional four field pelvic radiotherapy technique without computed tomography-treatment planning in cancer of the cervix: Potential geographic miss and its impact on pelvic control.Int. J. Radiation Oncology Biol. Phys vol. 31, No.1, pp.109-112; 1995.
10. Perez CA, Camel HM, Kuske RRet al.Radiation therapy alone in the treatment of carcinoma cervix: a 20 years' experience.Gynecol Oncol 23:127-40; 1986.
11. Greer BE, Koh WJ, Stelzer KJ, et al. An expanded pelvic radiotherapyfields for treatment of local-regionally advanced carcinoma of the cervix: outcomeand complications. Am J Obstet Gynecol 174:1141-50; 1996.
12. Le Bourgeois JP, Chavaudra J, Eschwege F et al. Cancers gynecologiques. In: Radiotherapie oncologique. Paris: Hermann Editeurs des Sciences et des Arts 253-67; 1992
13. Zunino S, Rosato O, Lucino S et al. Anatomic study of the pelvis in carcinoma of uterine cervix as related to the box technique. Int J Radiat Oncol Biol Phys. 44:53–9; 1994.
14. Justino PB, Baroni R, Blasbalg R et al. Clinical tumor dimensions may be useful to prevent geographical miss in conventional radiotherapy of uterine cervix cancer: A Magnetic Resonance Imaging- Based study. Int J Radiat Oncol Biol Phys.74:503–10; 2009.
15. Greer BE, Koh WJ, Figge DC et al. Gynecologic radiotherapy fields defined by intraoperative measurements. Gynecol Oncol. 38:421–4; 1990.
16. Yamazaki A, Shirato H, Nihioka T et al. Reduction of late complications after irregularly shaped four-field whole pelvic radiotherapy using computed tomographic simulation compared with parallel opposed whole pelvic radiotherapy. JPN J Clin Oncology 30: 180-184; 2000.
17. Y. S. Nagar, S. Singh, S. Kumar et al. Conventional 4-field box radiotherapy technique for cancer cervix: potential for geographic miss without CECT scan-based planning. Int J Gynecol Cancer 14, 865-870; 2004.
18. Robert Y. Kim, M.D., Andy Trotti, M.D. , Ching-Jung WV, M.D. et al.Radiation alone in the treatment of cancer of the uterine cervix: Analysis of pelvic failure and dose response relationship. Int J. Radiation Oncology Bio. Phys., Vol.17, 973-978; 1989.
19. Robert G Pearcey, Gavin C .E Stuart, M.D., Grant D Mac clean et al. Study to evaluate the toxicity and efficacy of Concurrent Cisplatin and Radiation Therapy in treatment of patients with locally advanced squamous cell carcinoma cervix. Gynecologic Oncology 58, 34-41:1995.
20. Chih-Jen Tseng, M.D., Chang-Ting Chang, M.D., Chyong-Huey Lai, M.D et al. Concurrent chemoradiotherapy and radiation therapy in advanced cervical cancer. Gynecologic oncology 66, 52–58; 1997.
21. M. King, C. McConkey, T. N. Latief et.al. Improved survival after concurrent weekly cisplatin and radiotherapy for cervical carcinoma with assessment of acute and late Side-effects. Clinical Oncology18, 38–45; 2006.
22. Sima Kadkhodayan, FatemehHomaeiShandiz, Mehdi SeilanianToussi et.al. Concurrent Chemo-radiotherapy without Brachytherapy in Locally Advanced Cervical Cancer. Iran J Cancer Prev. 4:195-200; 2013
23. Takahiro Oike, Tatsuya Ohno, Shinei Noda et al. Leukopenia by CCRT with innovator or generic cisplatin. Journal of Radiation Research. 54, 474-478; 2013.
24. L. Coia, MD, M. Won, MA, R. Lanciano, MD, et al.The Patterns of Care Outcome Study for Cancerof the Uterine Cervix.CANCER. December 15, 1990.