International Journal of Innovative Research and Advanced Studies (IJIRAS)
Volume 7 Issue 1, January 2020

ISSN: 2394-4404

Comparison Of Late Complications Following Conformal Four Field Radiotherapy And Whole Pelvic Radiotherapy In Cancer Cervix Patients

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Abstract: ***Late complication rates of four-field conformal pelvic radiotherapy using CT simulation were compared with those of whole pelvic radiotherapy using parallel opposed fields in cancer cervix patients in a non-randomized study.***

Methods: From March 2013 to December 2013, 74 patients who underwent radical chemoradiotherapy for clinical stage I, II or III squamous or adenosquamous cell carcinoma of the uterine cervix were treated with radiotherapy consisting of 50 Gy in 25 fractions in 5 weeks followed by 8Gy in 2 fractions of HDR brachytherapy. Thirty-four patients were treated with four-field 3D conformal technique following computed tomography (CT) simulation using beam's eye view and three-dimensional treatment planning with 15 MV photons on Linear accelerator. Forty patients received the conventional two-field technique, with CT simulation in 13 patients and X-ray simulation in 27 patients. There was no significant difference in patients' characteristics between the two groups.

Results: There was no statistical difference in survival, relapse-free survival or pelvic control rate between the two-field and four-field conformal radiotherapy groups with a mean follow-up period of 60 months. The actual 5-year pelvic control rate was 94% for the two-field technique and 100% for the four-field conformal technique. The incidence of grade II–III bowel complications in the four-field conformal technique group (2.9%, 1/34) was significantly lower than that in the two-field technique group (17.5%, 7/40) ($p < 0.05$). The actual 5-year complication rates of grade II bladder complications were 28.6 and 3.1% for the two-field technique and four-field conformal groups, respectively ($p = 0.0123$).

Conclusions: Four-field conformal pelvic radiotherapy using CT simulation appears to be as effective as parallel opposed whole pelvic radiotherapy with a lower incidence of bowel complication and bladder complications.

Keywords: uterine cervix cancer, radiotherapy, bowel complication, bladder complication, CT simulation, four-field conformal radiotherapy

I. INTRODUCTION

Radiation therapy plays a vital role in the management of carcinoma of the cervix. Carefully planned and executed radiation therapy yields excellent pelvic control and survival rates (1,2) Many stage IB1 cancers are treated equally effectively with radiation or radical surgery; most more advanced lesions are best treated with radiation. Although radiation alone can cure many patients with local-regionally advanced disease, recent studies have demonstrated that concurrent delivery of cisplatin-containing chemotherapy can improve the rates of local disease control and survival (3,4) However, treatment modality and technique must be individualized on the basis of clinical, anatomic, and social factors. Optimal treatment selection always requires close

ISSN: 2394-4404

cooperation between the patient's referring physician, gynecologic oncologist, and radiation oncologist.

Radiation therapy for intact carcinoma of the cervix usually involves a combination of EBRT and brachytherapy. The goal of treatment is to balance EBRT and brachytherapy in a way that maximizes the likelihood of local-regional tumor control while minimizing the risk of treatment complications. For many patients with local-regionally advanced disease, these treatments must also be carefully integrated with chemotherapy to achieve the greatest likelihood of cure.

The primary goals of EBRT are to sterilize regional disease and to shrink central tumor to facilitate subsequent brachytherapy. The degree of tissue penetration achieved by a radiation beam is related to the energy of the x-rays delivered from the radiation source. One of the earliest sources used for EBRT was Co 60, which produced a relatively deeply penetrating beam. However, linear accelerators now provide higher energy photon beams (15–25 MV) that are better suited for EBRT because they permit more homogeneous delivery of radiation to deep tissues with relative sparing of superficial tissues.

If a four-field technique is used, the anterior border of the field usually includes the anterior tip of the pubis; to cover the tumor, presacral nodes, and uterosacral ligaments, the posterior border usually includes S3 . Custom blocks may be used to shield anterior small bowel, soft tissue, and, in some cases, low rectum on the lateral fields. However, care must be taken not to shield potential sites of disease. Because the inguinal nodes drain the lower third of the vagina, they should be included in the treatment volume whenever the distal vagina is involved with tumor.

Whole-pelvis EBRT fields typically are designed with an upper border placed either at the L4-5 interspace. However, the fields may be extended superiorly if the para-aortic nodes are known to be involved or are believed to be at high risk for involvement. Because cervical cancer typically follows an orderly progression along the lymph node chain, the upper border is selected by balancing an estimate of the risk of disease at a given level against the expected morbidity from large-volume EBRT. In general, the upper border is placed at least 4–6 cm above known disease. This is probably sufficient if the patient has had a lymph node dissection with negative nodes above the level of involvement. Bulky or multiple nodes probably warrant greater extension of the fields, particularly if the patient has not had surgical evaluation of the nodes. Although the survival rate of patients with aortic node metastases is significantly less than that of patients with similar-stage disease who do not have this finding, about 20–40% of patients with aortic node metastases are curable with radiation alone, depending on the extent of pelvic disease.

COMPLICATIONS OF RADIATION THERAPY

Complications of radiation therapy are usually characterized as acute (occurring during or shortly after treatment), or late (occurring more than a few weeks and sometimes many years after radiation therapy). The acute complications of radiation therapy usually resolve within 2–3 weeks after completion of treatment.

Pelvic irradiation may cause acute proctosigmoiditis. Two to three weeks after the beginning of treatment, patients may develop diarrhea; on rare occasions, this may be associated with passage of blood and mucus or tenesmus. These symptoms usually subside shortly after the completion of EBRT. A small proportion of patients develop chronic diarrhea that may be associated with bleeding and anemia. In such cases, flexible sigmoidoscopy reveals a smooth pale mucosa with prominent friable blood vessels. The symptoms usually subside within a few months, although rarely patients develop chronic proctosigmoiditis that may lead to stricture or obstruction. In less than 5% of patients, radiation injury to the rectosigmoid may result in progressive ischemia leading to necrosis and occasionally stricture or fistula formation. When this occurs, patients should be carefully evaluated to exclude the possibility of recurrent disease. Patients who develop a radiation-induced rectovaginal fistula require a diverting colostomy. If there is no evidence of recurrent disease and the area of necrosis does not spread, selected patients may undergo resection of the involved area with a low reanastomosis of the sigmoid to the anus. However, the rate of anastomotic failure is high after this type of repair. Necrosis above the peritoneal reflection is rare but can be catastrophic if it leads to perforation with peritonitis or abscess formation. Early symptoms of this serious complication include abdominal pain, vomiting, bloody diarrhea, and weight loss and should be pursued aggressively.

The acute reaction of the small intestine to radiation therapy may also cause diarrhea and abdominal cramping. Nausea and vomiting are rare unless extended fields are used. These symptoms are usually well controlled with antidiarrheal medications and antiemetics and generally disappear within a few days of the completion of radiation. Diarrhea may also respond to a low-residue diet. Patients with a history of lactase deficiency may have particularly severe symptoms and may benefit from a lactose-free diet. Chronic, symptomatic small bowel injury rarely develops unless patients have a predisposing factor. Patients who have had extensive abdominopelvic surgery and those with a history of pelvic infection are particularly prone to develop small bowel injury following irradiation. Patients who are treated with extended fields or who received particularly high doses of pelvic radiation therapy are also more likely to suffer small bowel complications. The terminal ileum is most frequently involved. Patients who suffer chronic radiation-induced small bowel injury usually present 1–5 years after irradiation with symptoms of intermittent abdominal distention, cramping, nausea, weight loss, and diarrhea. The diarrhea is caused by rapid transit and malabsorption. Symptoms may wax and wane over a period of months to years. In less than 2% of patients who receive standard radiation doses, more severe injuries may develop, including focal stricture, obstruction, and, in severe cases, perforation. Recent studies have demonstrated that small bowel complications are significantly more frequent in women who smoke cigarettes, particularly those who smoke more than one pack of cigarettes per day.

Patients who have mild to moderate symptoms of small bowel obstruction can often be managed with a low-residue diet and careful observation. Patients with more severe symptoms, especially repeated episodes of partial obstruction,

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should receive surgical intervention. The obstructed portion of small bowel should be resected, preserving as much small bowel as possible. Intestinal bypass procedures should be performed only when resection is not technically feasible.

Approximately 5–10% of patients treated with pelvic radiation develop symptoms of dysuria and urinary frequency during EBRT for carcinoma of the cervix. When no infection is found, these symptoms usually respond to pyridium and resolve shortly after the completion of treatment. Although late radiation complications involve the bladder less frequently than the bowel, a small proportion of women will develop symptoms of radiation cystitis one or more years after radical radiation therapy. Some women will have only one or two episodes of sterile dysuria or mild hematuria. Rarely, radiation cystitis can cause hemorrhage requiring emergency intervention. After cystoscopy with clot evacuation, patients may benefit from continuous inpatient irrigation of the bladder with acetic acid or potassium permanganate solution or saline using a three-way Foley catheter. Extreme care should be taken to ensure that blood clots do not obstruct the outflow tract of the catheter during irrigation. Patients who do not respond to irrigation may be helped by electrocoagulation or bladder tamponade. Rarely, patients who have persistent bleeding may require cystectomy with urinary diversion.

A variety of other rare urinary tract complications may occur. After high doses of EBRT, women may develop a contracted fibrotic bladder, leading to frequent urination and, in some cases, incontinence. Severe radiation injury may result in focal necrosis leading to vesicovaginal fistula. When this occurs, a careful search for recurrent tumor is always indicated. Fistulae caused by radiation can rarely be repaired, and urinary diversion is usually required. Although ureteral obstruction usually indicates recurrent cervical cancer, it may rarely result from localized radiation fibrosis.

During radical radiation therapy for cervical cancer, the vaginal apex and superficial cervical tissues receive a high dose of radiation. It is not uncommon to see some degree of necrosis of these tissues in the weeks after treatment. In an attempt to rule out tumor recurrence, numerous biopsies are often performed, which may aggravate the tissue damage. Treatment of cervicovaginal necrosis should be conservative. Aggressive debridement may leave gaping uncorrectable defects. We recommend cleansing of the affected area with a solution of 50% peroxide and 50% water two to three times daily. Some believe that the addition of estrogen replacement therapy can assist in the healing process. After irradiation with high doses, the vaginal apex tends to become agglutinated. Vaginal stenosis and shortening tend to be more severe in patients who had large tumors or unfavorable (i.e. narrow) vaginal anatomy prior to irradiation. Regular intercourse or use of a vaginal dilator may help to maintain patency of the vaginal canal. Systemic and local application of estrogen reduces vaginal dryness. Because irradiation invariably eliminates normal ovarian function, estrogen replacement is needed for all young women who undergo pelvic irradiation to prevent osteoporosis and other sequelae of hypoestrogenism.

II. MATERIALS AND METHODS

From March 2013 to December 2013, 74 patients with clinical stage I, II or III squamous or adenosquamous cell carcinoma of uterine cervix were treated with radical chemoradiotherapy. The patients' characteristics are summarized in Table 1. Seventy-four patients received radical chemoradiotherapy. All patients were treated with radical chemoradiotherapy with 15MV photons in Linear Accelerator. 50 Gy in 25 fractions in 5 weeks followed by 8Gy in 2 fractions of HDR brachytherapy was delivered.

Beginning in March 2013, irregularly shaped four-field pelvic irradiation with CT simulation has been applied as a way of reducing the radiation dose to the small bowel and anterior abdominal wall (11). Thirty-four patients received conformal four-field pelvic irradiation consisting of the anterior, posterior and two lateral opposed fields using CT simulation. Forty patients received anterior–posterior parallel–opposed whole pelvic radiotherapy and these patients were investigated as the control group. The decision to use the two-field technique was according to the physician's preference rather than some rigid criteria.

In the X-ray simulation, the upper border was the intervertebral space between L4 and L5 and the lower margin was at the bottom of the obturator foramen. The lateral border was 1.5 cm lateral to the internal lateral rim of the bony pelvis and sacrum–iliac joint. In CT simulation, target volume was determined slice by slice for CT scan images of 1 cm slice thickness and 1 cm table shift. The upper border was defined to include the aortic bifurcation. The lateral border was defined to include the iliac artery and veins so that the relationship between the lead blocks and the bony structure was patient dependent. The lower border was determined by inclusion of the vaginal cuff. The clinical target volume included the anterior surface of the sacral bone and the external iliac and common iliac arteries and veins. The small bowel, anterior abdominal wall and anus were blocked by the beam's eye view using digitally reconstructed radiography. The planning target volume margin was 1 cm for the clinical target volume. Dose distribution was calculated three-dimensionally using Varian Eclipse software. As verification procedures, portal film was taken and compared with the simulation film in the X-ray simulation or the digitally reconstructed radiography in the CT simulation.

STATISTICAL ANALYSIS

Survival and relapse-free survival were calculated using the Kaplan–Meier method and compared using a generalized Wilcoxon test. Late complications were graded as grade I, II, III and IV for no requirement for medication, requirement for medical treatment, requirement for surgical treatment and death due to complications, respectively. The Kaplan–Meier method and chi-squared test were used for the comparison of late complications. The mean follow-up period was 108 months for the two-field technique and 55 months for the four-field technique. The patients in this study gave informed consent to the work

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III. RESULTS

Bladder complication was observed in 50% (20/40) of the patients in the two-field technique group; 25% (10/40) were grade I and 25% (10/40) were grade II and no patients experienced grade III complication (Table 2). Bladder complication was observed in 9% (3/34) of the patients in the conformal four-field technique group; 6% (2/34) were grade I and 3% (1/34) were grade II. The actual 5-year complication-free rates of grade II leg bladder complication were 71.4 and 96.9% for the two-field technique and four-field technique, respectively. The difference was statistically significant in a log-rank test ($p = 0.0123$). The time of onset of chronic bowel complication was difficult to determine, so the incidence of bowel complication after 6 months was compared without consideration of the time of its onset. Bowel complications were observed in 12 patients in the two-field technique group and six patients in the conformal four-field technique group (Table 2). The incidence of grade II–III bowel complications in the four-field technique group (0.0%, 0/34) was significantly lower than that in the two-field technique group (17.5%, 7/40) ($p < 0.05$). No other late complication was detected during the study period. In the two-field technique group, no difference was demonstrated in survival rates or pelvic control rates.

	Two-field	Four-field	Total
No of patients	40	34	74
Mean age (range) (years)	52 (31–78)	50 (29–62)	51 (29–78)
FIGO stage			
Ia (%)	0 (0)	0 (0)	0 (0)
Ib (%)	10 (25)	6 (18)	16 (22)
IIa (%)	1 (3)	6 (18)	7 (9)
IIb (%)	18 (45)	19 (56)	37 (50)
IIIa (%)	0 (0)	0 (0)	0 (0)
IIIb (%)	11 (28)	3 (9)	14 (14)
Mean follow-up (months)	108	55	

Table 1: Characteristics of patients

Bladder complication	Grade 1	Grade 2	Grade 3	Total
Two-field (%)	10 (25)	10 (25)	0 (0)	20 (50)
Four-field (%)	2 (6)	1 (3)	0 (0)	3 (9)
Bowel complication	Grade 1	Grade 2	Grade 3	Total
Two-field (%)	5 (13)	3 (8)	4 (10)	12 (30)
Four-field (%)	4 (12)	0 (0)	0 (0)	4 (12)

Grade 1, no requirement for treatment; grade 2, required medical treatment; grade 3, required surgical treatment.

Table 2: Late complications after Radical pelvic radiotherapy for uterine cervix carcinoma

IV. DISCUSSION

Pelvic radiotherapy for uterine cancer has been associated with high morbidity (12,13). The present study suggests that conformal four-field radiotherapy is useful for reducing the complication rate. This conclusion is consistent with previous reports about pelvic radiotherapy for uterus and prostate cancers (14–17). However, the present study is still an interim report in terms of late complications because the follow-up period is shorter for patients with four-field technique. Further follow-up is required to judge whether the superiority of four-fields technique is real.

The lower incidence of bowel complications following irregularly shaped four-field radiotherapy was consistent with the well-known fact that bowel complications can be reduced by minimizing the volume of bowel structure that receives doses higher than about 45 Gy (18).

Anatomical landmarks are not optimal to cover the lymphatics and may be suboptimal for a significant percentage of patients and could be a contributing cause of failure to control cervical cancer (14,20). Zunino et al. have confirmed that using the anterior border of the lateral fields over the anterior edge of the pubic symphysis and the posterior at the S2–3 interspace as the anatomic border of the lateral fields is inadequate in radical radiotherapy for uterine cervix cancer (10). X-ray simulation following pelvic organ opacification using contrast media was shown to be effective for conformal therapy, but the technique is time consuming and uncertainty is caused by bony landmarks (2). Kim et al. have suggested that CT simulation is required to decrease the potential geographic miss when using the four-field technique in radical radiotherapy for uterine cervical cancer (21). With the irregularly shaped four-field technique, the anterior border and posterior border can be determined using internal anatomy rather than bony structure in CT simulation. In the present study, it was not possible to analyze whether CT simulation was useful for reducing geographic miss because of the low incidence of pelvic relapses in both techniques. However, the high pelvic control rate of the irregularly shaped four-field technique in our series may be due to accurate coverage of the clinical target volume.Recent advances in the multileaf collimator on linear accelerators and 3D radiotherapy planning systems have made it practical to use more conformal fields than were employed with the technique used in this study (22). A further reduction of complication without deterioration in the tumor control rate can be expected using conformal four-field pelvic radiotherapy with a multileaf collimator.

In conclusion, conformal four-field pelvic radiotherapy using CT simulation appears to be as effective as parallel–opposed whole pelvic radiotherapy, with a lower incidence of bowel complication and bladder complcation.

ACKNOWLEDGEMENT

This study was conducted successfully with the help of our medical oncologist, gynec oncologist and other paramedical personnel and clerical staffs. I acknowledge their sincere efforts in conducting this study.

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