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Original Research Article

Complications of radiation therapy in carcinoma cervix

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Abstract
Radiotherapy (RT) is a key modality in treating carcinoma of cervix in all stages. Overall survival rates for patients with stage I and IIA cervical cancer treated with surgery or radiation usually range between 60% to 90%, suggesting that the two treatment modalities are equally effective. As with other modalities, the high cure rates with radiation therapy comes with some amount of complications. For patients with similar tumors, the overall rate of major complications is similar with surgery and radiotherapy, although urinary tract complications tend to be more common after surgical treatment (6-20%) and bowel complications (1-13%) are more common after radiotherapy. Complication rates tend to be higher when irradiation is combined with surgery. The chief complications noted after combined modality treatment are leg edema in approximately 15% cases, dysuria in 8% and positive urine culture in 20% cases. The dose of irradiation, technique, and the type of surgical procedure performed are important in determining the morbidity of combined therapy. With RT alone, complications differ with different techniques of radiation therapy and mainly depend on the stage of the disease, general condition of the patient, dose of radiation therapy, field arrangements, abdominal girth, dose rate, volume of irradiated tissue, expertise of the Radiation Oncologist and co-existing disease like inflammatory bowel diseases. Acute gastrointestinal side effects of pelvic irradiation are seen in about 41% and include diarrhea, abdominal cramping, rectal discomfort, & occasionally rectal bleeding, which may be caused by transient enteroproctitis. Genitourinary symptoms, secondary to cystourethritis, are dysuria, frequency, and nocturia. Erythema and dry or moist desquamation may develop in the perineum or intergluteal fold. The incidence of major late sequelae of radiation therapy for stage I and IIA carcinoma of the cervix ranges from 3% to 5%, and for stage IIB and III, between 10% and 15%. Five-year actuarial incidence of overall (all grades) and severe (grade 3/4) late toxicities in the rectum, bladder, small intestine and subcutaneous tissue may be as high as 12.3% and 1.1%, 11.2% and 1.2%, 9.2% and 0.2%, and 23.1% and 1.2%, respectively. Vaginal adhesions are seen in approximately 30% of cases and stenosis in one third of patients. With newer modalities like proton therapy, hadron therapy and inclusion of modern technological advancements in the radiation therapy planning, finding a cure for carcinoma of cervix with minimal complications is not too distant.

Keywords: complications, radiation therapy, carcinoma cervix

Introduction
Cancer of the uterine cervix is a major cause of cancer deaths in women worldwide accounting for an estimated 527,600 new cases and 265,700 deaths [1]. Although the incidence and mortality rates have declined, carcinoma cervix still ranks seventh in incidence and mortality in the world; and is the commonest malignancy in Asian women and constitutes approximately 30% of all cancers. It is also the leading cause of cancer mortality in India. GLOBOCAN 2012 reveals that every year 163,000 women are diagnosed with this particular kind of cancer and 67,000 die from the disease in India [2] The growing risk of cervical cancer in women in India (aged 0-64 years) is 2.4% compared to 1.3% for the world. Nearly 50% of the patients present with advanced stages (FIGO Stage III/IV) in India. Hence, carcinoma cervix remains a significant public health problem in India [2].
Treatment choices for cervical cancer is influenced by a number of factors, including tumor size, stage, histologic features, evidence of lymph node metastasis, risk factors for complications of surgery or radiotherapy, and patient preference. However, as a rule, high-grade intraepithelial lesions HSILs are managed with a loop electro-excision procedure (LEEP); micro-invasive cancers invading less than 3 mm (stage IA1) are managed with

conservative surgery (excisional conization or extrafascial hysterectomy [type I]) or intracavitary radiotherapy alone; early invasive cancers (stage IA2 and IB1 and some small stage IIA tumors) are managed with modified radical (type II) or radical (type III) hysterectomy or radiotherapy; and locally advanced cancers (stages IB2 through IVA) are managed with radiotherapy alone or in combination with concomitant cisplatin or carboplatin. Selected patients with centrally recurrent disease after maximum radiotherapy may be treated with radical exenterative surgery; isolated pelvic recurrence after hysterectomy is treated with irradiation. Evidence from randomized trials have led to the routine addition of concurrent cisplatin-containing chemotherapy to radiotherapy for patients whose cancers have a high risk of locoregional recurrence [3-5]. On the basis of 13 trials that compared chemoradiotherapy versus the same radiotherapy, there was a 6% improvement in 5-year survival with chemoradiotherapy. There was, however, the suggestion of a decreasing relative effect of chemoradiotherapy on survival with increasing tumor stage, with estimated absolute survival benefits of 10% (stage Ia to IIa), 7% (stage IIb), and 3% (stage III to IVa) at 5 years [6].

Overall survival rates for patients with stage I and IIA cervical cancer treated with surgery or radiation usually range between 60% and 90%, suggesting that the two treatments are equally effective [7, 8]. For patients with similar tumors, the overall rate of major complications is similar with surgery and radiotherapy, although urinary tract complications tend to be more common after surgical treatment and bowel complications are more common after radiotherapy [9-11].

However, biases introduced by patient selection, variations in the definition of stage IA disease, and variable indications for postoperative radiotherapy, concurrent chemotherapy, or adjuvant hysterectomy confound comparisons about the efficacy of radiotherapy versus surgery. Because young women with small, clinically node-negative tumors tend to be favored candidates for surgery and because tumor diameter and nodal status are inconsistently described in published series, it is difficult to compare the results reported for patients treated with surgery or radiotherapy. In 1997, Landoni *et al*. reported results from the only prospective trial comparing radical surgery with radiotherapy alone. In their study, patients with stage IB or IIA disease were randomly assigned to receive treatment with type III radical hysterectomy or a combination of external-beam and low-dose–rate intracavitary radiotherapy. With a median follow-up of 87 months, the 5-year actuarial disease-free survival rates for patients treated in the surgery and radiotherapy groups were 80% and 82%, respectively, for patients with tumors that were 4 cm or smaller and 63% and 57%, respectively, for patients with larger tumors. The authors reported a significantly higher rate of complications in the patients treated with initial surgery, and they attributed this finding to the frequent use of combined-modality treatment in this group [8].

Nature of Complications after Surgical Treatment of Carcinoma Cervix

The most frequent sequelae after radical hysterectomy is urinary dysfunction, as a result of partial denervation of the detrusor muscle. Patients may have various degrees of loss of bladder sensation, inability to initiate voiding, residual urine retention, and incontinence [3, 10]

Magrina reported some form of postoperative complications in 24% of the 375 patients treated with a modified radical hysterectomy (within 42 days) for various gynecologic disorders, Patients who had a pelvic lymphadenectomy experienced a greater incidence of lower extremity lymphedema (30—40%) than those who did not undergo this procedure. Other complications include ureterovaginal fistula (the incidence of which has decreased to <3%), hemorrhage, infection, bowel obstruction, stricture and fibrosis of the intestine or rectosigmoid colon, chronic rectal dysfunction and bladder and rectovaginal fistulas. Postsurgical complications are usually more amenable to correction than are late complications after irradiation [11]

Intraoperative and immediate postoperative complications of radical hysterectomy include blood loss (mean, 0.8 liter), ureterovaginal fistula (1% to 2% of patients), vesicovaginal fistula (less than 1%), pulmonary embolus (1% to 2%), small bowel obstruction (1% to 2%), and postoperative fever secondary to deep vein thrombosis, pulmonary infection, pelvic cellulitis, urinary tract infection, or wound infection (25% to 50%) [10, 11] Subacute complications include lymphocyst formation and lower-extremity edema, the risk of which is related to the extent of the node dissection. Lymphocysts may obstruct a ureter, but hydronephrosis usually improves with drainage of the lymphocyst [12].

Abrão *et al*. reported complications of surgical treatment in 302 patients with stage Ib and IIa cervical carcinoma submitted to radical hysterectomy and lymphadenectomy during the period from 1980 to 1994. The morbidity rate was 37.5% and the mortality rate 0.6%. The most common intraoperative complications were injuries to the great pelvic vessels and the most frequent postoperative complications involved the urinary tract. The leading causes of morbidity were urinary infection (20.8%), bladder dysfunction (9.2%) and ureteral fistulas (2.9%). Table-1 summarises the immediate post-operative complications of radical surgery [10-14].

Although most patients have transient decreased bladder sensation after radical hysterectomy, severe long-term bladder complications are infrequent with appropriate management. However, chronic bladder hypotonia or atony occurs in approximately 3% to 5% of patients, despite careful postoperative bladder drainage. The overall risk of major complications (particularly small bowel obstruction) is probably increased in patients who undergo postoperative pelvic irradiation. Matsuura *et al*. reported long-standing complications after treatment for cancer of the uterine cervix. The patients were divided into three groups: radical surgery alone (group A), radiotherapy alone (group B), and radical surgery with postoperative radiotherapy (group C). Dysuria was seen in 8%, and positive catheterized urine culture was noted in about 20% of groups A and C. Hydronephrosis was seen in 2% and 9% of groups A and B, respectively (Table-2). Colitis or ulcer detected by proctosigmoidoscopy was noted in 15%, 50%, and 43% of groups A, B, and C, respectively, frequently observed in radiotherapy group (P= 0.0029). Lymphocyst was still present in 6% of group A, and leg edema was noted in 14%, 6%, and 15% of groups A, B, and C, respectively as shown in Table-3 [11].

Ferrero *et al*. recently evaluated and reported toxicity of chemoradiation treatment (neoadjuvant, adjuvant and radical treatment) in patients diagnosed with cervix cancer. Acute gastrointestinal toxicity of grade 3 or more in 9 patients (17%) and haematological toxicity of grade 3 or more in 9 patients (17%). Chronic toxicity of grade 3 or more was

shown in only 2 patients (4%). The most frequent toxicities were gastrointestinal toxicity and haematological toxicity. The most frequent chronic toxicities were gastrointestinal toxicity and vaginal toxicity [12].

Complications of Combined Modality (Radiation followed by Radical Surgery) in Carcinoma Cervix

Complication rates tend to be higher when irradiation is combined with surgery, particularly because of injury to the ureter or the bladder (ureteral stricture or ureterovaginal or vesicovaginal fistula) [15]. The dose of irradiation, technique, and the type of surgical procedure performed are important in determining the morbidity of combined therapy. Jacobs *et al*. in 102 patients with invasive cervical carcinoma treated with low-dose preoperative irradiation and a radical hysterectomy with lymphadenectomy or high-dose preoperative irradiation and a conservative extrafascial hysterectomy, noted a major complication rate of 5% [16]. The incidence of complications is between 5% and 20%, depending on the extent of the para-aortic lymph node dissection, use of transperitoneal or retroperitoneal approach for the operation, and dose of irradiation given [15, 16].

Cetina *et al.* in a non randomized matched retrospective comparison of the results of treatment in patients treated with external beam chemoradiation (EBRT-CT) and radical hysterectomy versus those treated with identical chemoradiation followed by brachytherapy found similar progression free and overall survival in both the groups (N=80, median follow up= 26 months). The pattern of acute and late toxicities differed [14].

While in the group of patients receiving standard brachytherapy no acute complications were observed, in the surgical arm, the following acute complications were observed: postoperative infections, wound dehiscence, intraabdominal abscess, unilateral lymphocysts, ureterocutaneous fistula and hydronephrosis which required some form of urinary drainage (Table-1) [14].

However, the profile of late toxicity was different as shown in Table-4. In the surgery group there were 6 patients with hydronephrosis whereas no events were registered in the standardly treated arm, ($p < 0.016$). Proctitis was more common in the group of patients receiving standard EBRT-CT and brachytherapy. There were no differences however in the frequency and severity of cystitis ($p = 0.785$) [14].

Complication of Postoperative Irradiation in Carcinoma Cervix

When postoperative radiation therapy is given to selected patients, further complications of the additional therapy are expected because of intestinal adhesions to denuded surfaces in the pelvis. Enteric complications, such as obstruction, fistula, or dysfunction, were observed in 24% of patients reported by Fiorica *et al.* [17] In an evaluation of 98 patients undergoing radical hysterectomy for a nonadnexal gynecologic malignancy, the incidence of small bowel obstruction was significantly higher ($p <0.05$) in patients who received concomitant radiation therapy (20%). Findings at surgery consisted of minimal incisional adhesions but extensive matted small bowel adherent to the pelvic operative sites [3, 5].

Chen *et al*. studied survival and complications of combined modality treatment with surgery followed by post operative radiotherapy in patients with early invasive cervical cancer. The overall actuarial survival was 88%. Ten patients (18.5%) developed RTOG Grade 1–4 rectal complications. One of these patients received a colostomy for rectovaginal fistula, which was categorized as a Grade 4 rectal complication. The median time for the development of rectal complications was 12 months (range, 6–20 months) after radiotherapy. Five patients (9.3%) developed RTOG Grade 3–4 bladder complications, including one who received ileal conduit. Eight patients (14.8%) had RTOG Grade 1–4 non-rectal gastrointestinal complications, and one of these patients received laparotomy for severe abdominal pain. Two patients had lower-leg edema. Table-5 summarises the findings [18].

Thus, with radical surgery or combined modality the treatment outcomes is equivalent in carcinoma of cervix, but the profile of acute and late toxicity differs. Urinary complication tends to be more in surgical patients while small bowel and rectal complications are more frequent in those who receive pre or post operative radiation therapy [7-18].

Anatomical Considerations and Critical Organs in Radiation Therapy of Cervix Carcinoma

The uterus is a muscular hollow organ located in the midplane of the true pelvis, in an anteverted position, behind the bladder and in front of the rectum. The tolerance dose of the cervix and uterus is 200-300 Gy but the urinary bladder and rectum are the critical organs with low tolerance and limits delivery of high radiation dose to the cervix, if so delivered only at the cost of significant longterm complications that affects the quality of life of the patients [5]. TD5/5 for Urinary Bladder and Rectum is 65 Gy and 60 Gy (100 cc volume) respectively [19].

American Brachytherapy Society recommends treating Point A to at least a total low-dose-rate (LDR) equivalent of 80-85 Gy for early stage disease and 85-90 Gy for advanced stage. As with LDR brachytherapy, every attempt should be made to keep the bladder and rectal doses below 80 Gy and 75 Gy LDR equivalent doses, respectively [20]

Principles of Radiation Effects on Normal Tissues

No treatment comes without any complication; the same is true for radiation therapy as well as the surgical treatment for carcinoma of the cervix. The complications of radiation therapy are classified by the Radiation Therapy Oncology Group (RTOG) as

I. Acute Tissue Reactions

Acute tissue reactions typically occur during treatment or shortly thereafter (upto 90 days of treatment)**,** and they are really just related to the acute toxicity of the treatment from the radiation therapy. They generally resolve shortly after termination of the therapy, but they are significant in that they significantly affect the patient's quality of life during the therapy, and they can become severe enough to interfere with treatment. Acute tissue reactions typically occur at sites where there are rapidly proliferating cells such as mucosal sites (eg. Small intestines) or skin [21].

II. Late Tissue Reactions

The late tissue reactions are defined in the literature as occurring more than 90 days after treatment (Table-6). These are more often permanent and frequently irreversible complications, they tend to be more severe, and they tend to affect slowly dividing cells such as Neurons, Rectum and Urinary bladder [21].

Acute Complications of RT Alone in Carcinoma Cervix

Descriptions of sequelae vary among institutions because toxicity grading scales are not uniform and the scoring system for complications is not clearly stated in all reports. The acute sequelae may be life threatening complications occurring as a result of the treatment procedure, co-morbid conditions, immobilization or due to anesthesia; and non fatal complications which are expected but the degree of which may vary from patient to patient. These affect the quality of life of the patient and sometimes severe enough to even interrupt or abandon the treatment.

Dusenbery *et al.* reported 21 (6.4%) life-threatening complications in 327/462 patient implants. [22] Lanciano *et al.* in 95 tandem and ovoid insertions for cervical cancer in 91 patients observed two uterine perforations and a vaginal laceration in two patients. Eighteen percent of implants in 16 patients were associated with temperatures higher than 100.5°F. Five implants (5%) were removed because of presumed sepsis, pulmonary disease, arterial hypotension, change in mental status, and myocardial infarction [23]

Jhingran and Eifel, in 4,043 patients with carcinoma of the cervix who had undergone 7,662 intracavitary procedures, observed 11 (0.3%) documented or suspected thrombo-embolism, resulting in four deaths; the incidence of post implant thrombo-embolism did not decrease significantly with the routine use of minidose heparin prophylaxis. Other life-threatening perioperative complications included myocardial infarction (one death in five patients), cerebrovascular accident (two patients), congestive heart failure (three patients), and halothane liver toxicity (two deaths). Intraoperative complications included uterine perforation (2.8%) and vaginal laceration (0.3%), which occurred more frequently in patients 60 years of age or older ($p < 0.01$) [24].

Shah *et al.* reported bowel puncture noted in 26 patients and bladder puncture noted in 19 out of 36 patients treated with interstitial brachytherapy for carcinoma cervix. However, No patients with bowel puncture experienced Grade 2 or greater acute gastrointestinal toxicity and only 1 had Grade 3 or greater late gastrointestinal toxicity. No patients with bladder puncture experienced greater than Grade 2 acute genitourinary toxicity and only 2 had late Grade 3 or greater genitourinary toxicity [25]. Table-7 summarises the life threatening complications of radiation therapy in carcinoma cervix [23-25]

Most common morbidity during hospitalization in patients with cervical carcinoma undergoing LDR intracavitary brachytherapy insertions were fever/infection (14.1%) or gastrointestinal problems (5.9%) and overall (24.7%) [5].

Acute gastrointestinal side effects of pelvic irradiation include diarrhea, abdominal cramping, rectal discomfort, and occasionally rectal bleeding, which may be caused by transient enteroproctitis. Patients with hemorrhoids may experience discomfort earlier than other patients. Kim *et al.* reported Forty six percent of patients experienced early bowel complications, most of which were grade 1 or 2 and relieved spontaneously or by medication; 25 patients (38%) with grade 1 or 2, 4 patients (6%) with grade 3 and 1 patient (2%) with grade 4. The complications usually began to occur 3 weeks after the commencement of radiotherapy. The actuarial incidence of early bowel complications was 41% at 10 weeks after commencement of RT [26].

Diarrhea and abdominal cramping can be controlled with the oral administration of diphenoxylate hydrochloride, with loperamide, atropine sulfate, or opium preparations or emollients such as kaolin and pectin. Proctitis and rectal discomfort can be alleviated by small enemas with hydrocortisone and anti-inflammatory suppositories containing bismuth, benzyl benzoate, zinc oxide, or Peruvian balsam. Some suppositories contain cortisone. Small enemas with cod liver oil are also effective. A low-residue usually helps to decrease gastrointestinal symptoms [5, 26].

Genitourinary symptoms, secondary to cystourethritis, are dysuria, frequency, and nocturia. The urine is usually clear, although there may be microscopic or even gross hematuria. Methenamine mandelate and antispasmodics such as phenazopyridine hydrochloride or a smooth muscle antispasmodic such as flavoxate hydrochloride, hyoscyamine sulfate, oxybutynin chloride, or tolterodine tartrate can relieve symptoms. Fluid intake should be at least 2,000 to 2,500 mL daily. Urinary tract infections may occur; diagnosis should be established with appropriate urine culture studies, including sensitivity to sulfonamides and antibiotics. Therapy should be promptly instituted [3, 5, 26].

Erythema and dry or moist desquamation may develop in the perineum or intergluteal fold. Proper skin hygiene and topical application of petroleum jelly, petrolatum, or lanolin should relieve these symptoms. U.S.P. zinc oxide ointment and intensive skin care may be needed for severe cases [5].

Management of acute radiation vaginitis includes douching every day or at least three times weekly with a mixture of 1:5 hydrogen peroxide and water. Douching should be continued on a weekly basis until the mucositis has resolved or for 2 or 3 months as necessary. Superficial ulceration of the vagina responds to topical (intravaginal) estrogen creams, which stimulate epithelial regeneration within 3 months after irradiation. Use of vaginal dilators several times daily, started during the course of treatment, prevents vaginal stenosis. Psychoeducational intervention and motivation improve the compliance in use of dilators. More severe necrosis may require debridement on a weekly basis until healing takes place (Table-8) [5, 26].

Ferrero *et al.* evaluated toxicity of chemoirradiation treatment in patients diagnosed with cervix cancer. Acute gastrointestinal toxicity of grade 3 or more in 9 patients (17%) and haematological toxicity of grade 3 or more in 9 patients (17%). Similar results were reported by Celina *et al.* after chemoradiation with cisplatin (Table-9). Though chemoradiation increases absolute 5 year survival by 6% but the acute toxicity is increased by 2-10 folds [6, 12, 14].

Late Sequelae of RT in Carcinoma Cervix

The LENT Paradigm

Late effects syndromes at each organ site are not random events, but are specific entities that occur at certain times, are expressed in a recognizable fashion and, in many cases, can be ameliorated. A paradigm can be outlined that guides the clinical radiation oncologist to arrive at a correct diagnosis and management of specific complications. This 10-step diagnosis process is designated as the Late Effects of Normal Tissue (LENT) paradigm and includes the following [21]:

- Clinical detection: Characteristic signs and symptoms that herald the onset of radiation-induced toxicities.
- Time course of events: Recognition of the clinical pathologic time course, including the onset of subclinical and overt abnormalities.
- Dose/time/volume: Identification of the relevant radiation parameters, with determination of whether

these factors explain the sequelae under consideration.

- Chemical/biologic modifiers: Identification of other relevant treatment components.
- Radiologic imaging: Discernment of the abnormalities on imaging techniques.
- Laboratory tests: Definition of the associated laboratory abnormalities.
- Differential diagnosis: Distinction of therapy-associated sequelae from recurrence or metastatic cancer in the first 5 years, other degenerative or inflammatory diseases from 5 to 10 years, and second malignant tumors after 10 years.
- Pathologic diagnosis: Consideration for tissue diagnosis of the adverse effect to confirm its presence versus disease recurrence or second malignant tumors.
- Management: Use of restorative, ameliorative, or prophylactic treatment in the form of either medical or surgical intervention.
- Follow-up: Consideration for nursing and medicolegal aspects.

The incidence of major late sequelae of radiation therapy for stage I and IIA carcinoma of the cervix ranges from 3% to 5%, and for stage IIB and III, between 10% and 15%. The most frequent major sequelae for the various stages are listed in Table-10. Injury to the gastrointestinal tract usually appears within the first 2 years after radiation therapy, whereas complications of the urinary tract are seen more frequently 3 to 5 years after treatment [3-26].

Perez *et al*. reported that with doses below 75 to 80 Gy delivered to limited volumes, grade 2 and 3 complications in the urinary tract and rectosigmoid were approximately 5%. However, the incidence increased to over 10% with higher doses of irradiation to these organs. Doses higher than 60 Gy were also correlated with a greater incidence of small bowel injury. The same analysis showed that patients who experienced sequelae of therapy had slightly better survival rates than patients without any complications [5].

The incidence of hemorrhagic cystitis was 6.5% with stage IB carcinoma of the cervix treated with irradiation, 23% had grade 2 (repeated minor bleeding), and 18% grade 3 (hospitalization required for medical management). The median interval to onset of hematuria was 35.5 months. Minor episodes of hematuria are managed by antibiotic therapy. Cystoscopic, laser, or cautery treatment of bleeding points is indicated. Clot evacuation and continuous bladder irrigation are important elements in the acute management of patients with heavy bleeding. Occasionally, a urinary diversion is required for intractable severe hematuria. With hemorrhagic radiation cystitis, significant improvement was observed after treatment with hyperbaric oxygen [5, 12, 13].

Ureteral stricture at 20 years was observed in 2.5% of 1,784 patients with carcinoma of the cervix treated with irradiation. The most common presenting symptoms were flank pain and urinary tract infection. Treatment of ureteral stenosis may consist of stenting or resection of the fibrotic segment and reimplantation of the ureter either with a ureteroneocystostomy or ureteroileocystostomy. In approximately half of the patients, diversion of urinary stream and ileal conduits is necessary. Occasionally, a nephrectomy is performed for removal of a nonfunctional kidney [5, 15, 25].

Up to 88% of women treated with pelvic radiation for cervical cancer develop vaginal stenosis as a consequence of therapy. Grigsby *et al*. described complex problems with sexual adjustment in women with gynecologic tumors treated with radiation therapy; with decreased frequency of sexual intercourse, desire, orgasm, and enjoyment of intercourse in 16% to 47% of patients. Regular vaginal dilation is widely recommended to maintain vaginal health and sexual functioning; however, the compliance rate with this recommendation is not consistent. Potential measures to prevent and treat stenosis are topical estrogen, topical benzydamine and systemic hormones [12, 18, 27].

The cumulative actuarial incidence of femoral neck fracture was 11% at 5 years and 15% at 10 years. Most of the fractures occurred in patients receiving 45 to 63 Gy [27].

Uterine necrosis is a rare subacute complication of chemoradiation in carcinoma cervix manifesting as severe pelvic pain and persistent vaginal bleeding. The diagnosis is confirmed by biopsy without evidence of tumor. The management can be complex and may even require a total abdominal hysterectomy [28].

Patel FD reported an audit on evaluation of late toxicities of patients with carcinoma of the cervix treated with radical radiotherapy in India. One thousand and sixty nine women with carcinoma of the cervix (stage I-IVA) were treated at their centre with external-beam radiotherapy (EBRT) and intra-cavitary radiotherapy (ICRT) (n = 871) or EBRT alone (n = 198). Median follow-up was 34 months. Median dose to point A was 81 Gy. Five-year actuarial incidence of overall (all grades) and severe (grade 3/4) late toxicities in the rectum, bladder, small intestine and subcutaneous tissue were 12.3% and 1.1%, 11.2% and 1.2%, 9.2% and 0.2%, and 23.1% and 1.2%, respectively. Vaginal adhesions were seen in 29.6% of cases and stenosis in 33.9% of cases. Subcutaneous fibrosis was significantly higher in patients with AP separation over 18 cm, those treated by cobalt machines and those who received EBRT only. Severe subcutaneous fibrosis was influenced by the use of EBRT alone. Overall incidence of vaginal toxicity was higher in women whose overall treatment time (OTT) was shorter and in women who received ICRT. Vaginal stenosis was higher in elderly women and in women who received ICRT by low dose rate (Table-11). The author concluded that with telecobalt machines, impressive results with acceptable late toxicity can be achieved in the treatment of cancer of the cervix using an ideal combination of EBRT with ICRT [27].

Complications with High Dose Rate (HDR) Versus Low Dose Rate (LDR) Brachytherapy

The late complications with HDR brachytherapy tend to be more than the LDR but with proper technique, optimization, separation (rectal and urinary bladder) and low dose more fractionated schedules, they are equivalent (Table-12) [5].

Patel FD reported overall local control in the low dose rate group of 79.7% as compared to 75.8% in the high dose rate group. The 5 years survival figures in the low dose rate and high dose rate group were also comparable. The only statistically significant difference was found in the incidence of overall rectal complications which was 19.9% for the low dose rate group as compared to only 6.4% for the high dose rate group. However, the more severe grade 3-4 complications were not significantly different between the two groups (2.4% vs. 0.4%, respectively). The bladder morbidity in both the groups was similar [30].

Clark *et al*. reported on 43 patients treated with pelvic EBRT (46 Gy) and three HDR intracavitary treatments given weekly combined with concomitant chemotherapy (cisplatin,

30 mg/m^2 weekly) for advanced carcinoma of the cervix. At 40 months after treatment, 9/13 patients who received a dose to the rectal reference point greater than the prescribed point A dose had a 46% actuarial rate of serious (grade 3 and 4) rectal complications, compared with 14% in the remainder. A strong dose response was observed with a threshold for complications at a brachytherapy dose of 8 Gy per fraction [31].

Complications with Different Schedules of High Dose Rate Brachytherapy

Hellebust *et al*. compared the severe late effects (Grade 3 or greater) for two groups of cervical cancer patients treated with the same external beam radiotherapy and two high-dose-rate intracavitary brachytherapy regimens and to investigate the influence of the dose delivered each week. For 120 patients, intracavitary brachytherapy was delivered with 33.6 Gy in eight fractions to Point A (HD group), and for 119, intracavitary brachytherapy was delivered with 29.4 Gy in seven fractions to Point A (LD group).

The actuarial rate of developing severe gastrointestinal morbidity at 7 years was 10.7% and 8.3% for HD and LD groups, respectively. The rate for genitourinary morbidity was 6.6% for the HD group and 5.0% for the LD group, respectively. No significant difference was found between the two groups. He concluded that 20 Gy/wk is an upper tolerance level when the dose to the International Commission on Radiation Units and Measurements rectum point is 81Gy$_{\alpha/\beta=3}$ (isoeffective [equivalent] dose of 2-Gy fractions) [32].

Chatani *et al*. evaluated a total of 218 patients with carcinoma of the uterine cervix treated. For 98 patients, intracavitary brachytherapy was delivered with 6–7.5 Gy/fraction to Point A (Group A), and for 120, 5 Gy/fraction with a modified source step size (Group B). The 3-year cause-specific survival rates by stage and treatment schedule were Group A: 91% and Group B: 96% in Stage I, 89% and 92% in Stage II, 64% and 75% in Stage III, 44% and 69% in Stage IV. The survival curves did not reveal any statistically significant differences at any stage. The 3-year cumulative local failure rates were 14% in Group A and 7% in Group B (P = 0.1202), while the actuarial rates of developing rectal complication (Grade 2 or more) at 3 years were 25% in Group A and 4% in Group B ($P < 0.0001$) [33].

Complications with Intracavitary versus Interstitial High Dose Rate Brachytherapy

Interstitial implant yielded better parametrial coverage and with fewer dose to rectal and bladder volumes. For IIIB disease tumor response and 3-year local control were significantly higher with interstitial treatment with significantly less parametrial failure in a study by Sahu *et al.* [34].

Intensity Modulated Radiation Therapy (IMRT) in Carcinoma Cervix

Intensity modulated radiation therapy (IMRT) and 3D-CRT have the potential to deliver adequate dose to the target structures while sparing the normal organs and could also allow for dose escalation to grossly enlarged metastatic lymph node in pelvic or para-aortic area without increasing gastrointestinal/genitourinary complications. Portelance conducted a dosimetric analysis to determine if IMRT can meet these objectives in the treatment of cervical cancer. The small bowel dose was reduced by about 20%, rectal and Bladder dose by 40-50% as compared to two field or 4-field conventional EBRT. But no randomized clinical trial has reported its results yet [35].

Xu *et al.* examined the safety of Extended Field IMRT in cancer cervix and found the volume of the duodenum receiving 55 Gy (V55) to be an important dosimetric predictor of duodenal toxicity. The mean dose delivered to 2 cm^3 of the duodenum was 34.9 Gy (range, 0-52.3 Gy) and 50.1 Gy (range, 31.3 - 58.3 Gy), respectively. Grade 3 acute gastrointestinal toxicity was recorded in 3.9% (n = 3) of patients [36].

Hence, IMRT can serve for simultaneous integrated boost, for conformal avoidance of conventional EBRT and for extended Field IMRT with low duodenal dose, but its use in cancer cervix is yet to be validated.

Dose Volume Considerations to Predict Complications for RT in Carcinoma Cervix

Small Intestine

The threshold for minimal effect is 50 Gy, but there is a steep dose-response curve using daily conventional fractions of 1.8 to 2 Gy. The incidence of small bowel injury is 15% to 25% if paraaortic irradiation doses are 50 to 55 Gy whereas 45 to 50 Gy is well tolerated. Perez and colleagues found a 1% incidence of small bowel toxicity with a pelvic sidewall dose of 50 Gy and a 5% incidence at >70 Gy; fractionated doses induce a 15% increased incidence of severe late complications when more than 2 Gy per fraction is used. Eifel and associates in a 20-year follow-up study of patients with cervical cancer, noted an increase in the complication rate over time [5, 19, 32, 36].

Colo-rectum

In patients with cervical cancer who have received external irradiation and brachytherapy The incidence of severe proctitis in patients with cancer of the cervix is dose-dependent: There is a <4% incidence with doses of <80 Gy, a 7% to 8% incidence after 80 to 95 Gy, and a 13% incidence for doses of 95 Gy [37].

Ogino *et al*. in patients with invasive carcinoma of the cervix treated with HDR brachytherapy, noted that grade 4 rectal complications were not observed in patients with biologic equivalent dose lower than 147, assuming an α/β ratio of 3 Gy for late reactions [38].

Dose Response Relationship with Critical Organs in Treatment of Carcinoma Cervix

RTOG Grade III rectosigmoid complications are seen in 1-4% cases receiving < 80 Gy (LDR equivalent dose) and in 9% cases receiving ≥ 80 Gy to rectal point. Similarly RTOG grade III Urinary sequelae occurs in 2% cases receiving < 70 Gy and in 5% cases receiving ≥ 75 Gy to the urinary bladder point. Grade III small bowel complications are seen in 1% cases receiving ≤ 50 Gy and in 2% to 4% cases receiving > 60 Gy to the small intestines [35-37].

DVH Correlates

Small Intestine: DVH Correlates

Acute GI toxicity correlates with small bowel dose % volume of small intestine receiving doses in the range of 75 - 100% of prescribed dose significant predictor. In a study of

50 patients Volume of small bowel receiving 100% of prescribed dose retained significance in multivariate analysis [33-38].

Colorectum: DVH Correlates

Anal Canal Dysfunction

Correlated with radiation doses in the range from 50-60 Gy.

Rectal Dysfunction

Risk of late rectal bleeding increases significantly when the rectum (>1 cm length) is enclosed by the 50-60 Gy isodose curve.

Bone Marrow: DVH correlates

Significant correlation of volume of bone marrow receiving a dose of >10 Gy is seen [38].

Geometrical Sparing Factor (GSF)

The geometrical sparing factor (GSF) is defined as the ratio between an effective normal tissue dose and an effective tumor dose. A smaller GSF with greater normal tissue sparing helps in allowing HDR-ICB to be performed with relatively few fractions. Patients with rectal GSF greater than 0.7 or bladder GSF greater than 0.9 are at risk for grade 2 and higher late sequelae [39]. American Brachytherapy Society (ABS) has recommended reduction in the effective dose to Rectum/Bladder tissues to about 80% of the point a dose [20].

IGBT in Carcinoma Cervix

MRI-based brachytherapy remains the gold standard for IGBT because of its high-soft tissue resolution allowing accurate delineation of the gross tumor and possible tumor invasion of adjacent normal organs. GEC-ESTRO guidelines are followed. Among 141 cervical cancer patients stage IB–IVA who had MRI-based IGRT according to GEC-ESTRO guidelines, local control was achieved in 134 patients (95%) at a median follow-up of 51 months. update of the study demonstrated a relationship between the dose to the rectum and late toxicities. Normal OAR DVH illustrates the dose to 2 cc (D2cc), 1 cc (D1cc), and 0.1 cc (D0.1cc) of the bladder and rectum from both external beam and brachytherapy. Grade 2–4 rectal side effects occurred in 5, 10, and 20% of patients for rectal D2cc of 67, 78, and 90Gy, respectively [40]. There was no significant correlation between bladder dose and late toxicities.

Adaptive planning in case of tumor regression between sequential brachytherapy sessions may further decrease the risk of complications because of a decreases radiation dose to the normal organs adjacent to the tumor [41].

The EMBRACE and Retro-EMBRACE study will further establish a benchmark for clinical outcome with regard to control of the tumor's growth, patient survival, adverse effects of treatment and quality of life.

Table 1: Immediate Post-Operative Complications of Radical Hysterectomy

Complications	Incidence
Overall morbidity	37%
Mortality	Less than 1%
Blood loss (mean, 0.8 liter)	Most cases
Urinary dysfunction	10%
Urinary tract infection	21%
Ureterovaginal fistula	1-2.9%
Vesicovaginal fistula	less than 1%
Pulmonary embolus	1-2%
Small bowel obstruction	1-2%
Infection	7.5%
Wound dehiscence	2.5%
Intraabdominal abscess	2.5%
Lymphocyst formation	12.5%
Ureterocutaneous Fistula	2.5%
Hydronephrosis	10%
Lower-extremity edema	30—40%
Postoperative fever secondary to • deep vein thrombosis • pulmonary infection • pelvic cellulitis • urinary tract infection, or • wound infection	25-50%

Table 2: Urologic Complications after Treatment in Carcinoma Cervix Surgery versus RT versus Combined

Complications at 5-years	Group A (RAH*, n=51) (%)	Group B (RT, n=32) (%)	Group C (RAH+RT, n=26) (%)
Dysuria	8	0	8
Microhematuria	10	13	12
Hydronephrosis	2	9	0
Vesicovaginal fistula	0	3	0
Positive catheterized urine culture	23	0	19

*RAH=Radical Abdominal Hysterectomy

Table 3: Bowel Complications after Treatment in Carcinoma Cervix Surgery versus RT versus Combined

	Group A (RAH, n=51) (%)	Group B (RT, n=32) (%)	Group C (RAH+RT, n=26) (%)
Anal bleeding	6	25	19
Colitis or ulcer	15	50	43
Ileus	2	0	0
Rectovaginal fistula	0	3	0
Lymphocyst	6	0	0
Leg edema	14	6	15

Table 4: Late Complications in Carcinoma Cervix Pre-op RT → Surgery versus Radical RT alone

	Combined modality RT → Radical Surgery n=40				Radical RT alone EBRT plus Brachytherapy n=40				P value
Toxicity	I	II	III	IV	I	II	III	IV	
Hydronephrosis*	7.5%	7.5%	0	0	0	0	0	0	0.016
Proctitis**	2.5%	7.5%	0	0	2.5%	25%	2.5%	2.5%	0.008
Cystitis**	0	2.5%	5%	0	0	0	5%	2.5%	0.785

*CTC NCI version 2
**RTOG Late morbidity scoring criteria

Table 5: Late Complications of Combined Modality Treatment Surgery → Post-op RT

Organ	Percentage (n=54)	Median Time to complication (Median Follow up=58 mo)
Rectal		12 mo
Grade 1 & 2	(9/54) 16.67 %	
Grade 3 & 4	(1/54) 1.85 %*	
Non Rectal GI		14 mo
Grade 1 & 2	(7/54) 13 %	
Grade 3 & 4	(1/54) 1.85 %**	
Bladder		26 mo
Grade 1 & 2	Nil	
Grade 3 & 4	(5/53) 15 %	
Lower leg edema	(2/54) 3.70%	

*Rectovaginal fistula
**Required laparotomy

Table 6: RTOG* Radiation Morbidity Scoring Criteria

Late radiation morbidity scoring criteria					
Organ	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Rectum	Mild diarrhea Mild cramping Bowel movement 5 times daily Slight rectal discharge or bleeding	Moderate diarrhea and colic Bowel movement >5 times daily Excessive rectal mucus or intermittent bleeding	Obstruction or bleeding requiring surgery	Necrosis/ Perforation/ Fistula	Death resulting from the toxicity
Bladder	Slight epithelial atrophy Minor telangiectasia (microscopic hematuria)	Moderate frequency Generalized telangiectasia Intermittent macroscopic hematuria	Severe frequency and dysuria Severe generalized telangiectasia (often with petechiae) Frequent hematuria Reduction in bladder capacity (<150 cc)	Necrosis/ Contracted bladder (capacity <100 cc) Severe hemorrhagic cystitis	Death resulting from the toxicity
Acute Radiation Morbidity Scoring Criteria					
Rectum	Increased frequency or change in quality of bowel habits not requiring medication/ rectal discomfort not requiring analgesics	Diarrhea requiring parasympatholytic drugs (e.g., Lomotil)/ mucous discharge not necessitating sanitary pads/ rectal or abdominal pain requiring analgesics	Diarrhea requiring parenteral support/ severe mucous or blood discharge necessitating sanitary pags/abdominal distention (flat plate radiograph demonstrates distended bowel loops)	Acute or subacute obstruction, fistula or perforation; GI bleeding requiring transfusion; abdominal pain or tenesmus requiring tube decompression or bowel diversion	Death resulting from the toxicity

Bladder	Frequency of urination or nocturia twice pretreatment habit/ dysuria, urgency not requiring medication	Frequency of urination or nocturia which is less frequent than every hour. Dysuria, urgency, bladder spasm requiring local anesthetic (e.g., Pyridium)	Frequency with urgency and nocturia hourly or more frequently/ dysuria, pelvis pain or bladder spasm requiring regular, frequent narcotic/gross hematuria with/ without clot passage	Hematuria requiring transfusion/ acute bladder obstruction not secondary to clot passage, ulceration or necrosis	Death resulting from the toxicity

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Table 7: Life Threatening Complications of RT in Treatment of Carcinoma Cervix

Study	Complications	Incidence (%)	Remark
Dusenbery *et al*.	Overall	21/327 (6.42%)	
Lanciano *et al*.	Uterine perforations	2/91 (2.19%)	
	Vaginal lacerations	2/91 (2.19%)	
	Fever (>100.5°F)	16/91 (17.9%)	
	Others (Sepsis, MI, pulmonary disease, arterial hypotension and change in mental status)	5/91 (5.26%)	
Eifel *et al*. (n=4042)	Thromboembolism		Death in 4 patients
	MI	5 (0.15%)	Death in 1 patient
	CVA	2 (0.05%)	
	CHF	3 (0.075%	
	Halothane liver toxicity (Anaethesia)	2 (0.05%)	Both died
	Vaginal laceration	11 (0.3%)	
	Uterine perforation	113 (2.8%)	
Shah *et al*. (Interstitial brachytherapy)	Bowel puncture	26/36 (72.2%)	None developed Grade 2 or more acute GI toxicity
	Bladder puncture	19/36 (52.8%)	None developed Grade 2 or more acute GU toxicity

Table 8: Acute Toxicities of RT in Carcinoma Cervix and Its Management

Toxicity	Incidence	Management
Acute Lower GI Toxicity	41%	Diarrhoea and abdominal cramps: • Low residue diet with no grease or spices and increased fiber (psyllium, polycarbophil). • Oral administration of diphenoxylate hydrochloride, with loperamide, atropine sulfate, or opium preparations or emollients such as kaolin and pectin. Proctitis and rectal discomfort can be alleviated by • Small enemas with hydrocortisone and anti-inflammatory suppositories containing bismuth, benzyl benzoate, zinc oxide, or Peruvian balsam. • Small enemas with cod liver oil are also effective.
Acute Genitourinary Symptoms	28%	• Fluid intake should be at least 2,000 to 2,500 mL daily. • Methenamine mandelate and antispasmodics such as phenazopyridine hydrochloride or a smooth muscle antispasmodic such as flavoxate hydrochloride, hyoscyamine sulfate, oxybutynin chloride, or tolterodine tartrate can relieve symptoms. • Urinary tract infections may occur; diagnosis should be established with appropriate urine culture studies, including sensitivity to sulfonamides and antibiotics. Give antibiotics.
Acute Skin Toxicity	31%	• Proper skin hygiene and topical application of petroleum jelly, petrolatum, or lanolin relieve these symptoms. • Zinc oxide ointment and intensive skin care may be needed
Acute Radiation Vaginitis	37%	• Douching every day or at least three times weekly with a mixture of 1:5 hydrogen peroxide & water; and continued on a weekly basis until the mucositis has resolved or for 2 or 3 months as necessary. • Superficial ulceration of the vagina responds to topical (intravaginal) estrogen creams within 3 months after irradiation. • Use of vaginal dilators several times daily, started during the course of treatment, prevents vaginal stenosis. • Psychoeducational intervention and motivation. • Severe necrosis may require debridement on a weekly basis until healing.

Table 9: Acute toxicity of Chemoradiation in Carcinoma Cervix (RTOG* Grades)

	Acute Toxicity RTOG grades (N=83)				
Toxicity	0	I	II	III	IV
Upper GI	2.5%	56.5%	36%	5%	0
Lower GI	21%	29%	44%	6%	0

Genitourinary	53.25%	40.5%	2.5%	3.75%	0
Leucocytes	2.5%	17.25%	42.5%	38.75%	0
Hemoglobin	57%	27.5%	13%	2.5%	0
Platelets	90%	5%	2.5%	2.5%	0

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Table 10: Late Complications of RT in Carcinoma Cervix: Grade 2 Sequelae

	Stage				
	IB	**IIA**	**IIB**	**III**	**IVA**
Total no. of patients treated	415	137	391	326	23
Number of complications	51 (12%)	14 (10%)	65 (17%)	38 (12%)	3 (13%)
Rectum-rectosigmoid	-	-	-	-	-
Rectal stricture	-	1	2	1	1
Proctitis	8	1	13	6	-
Rectal ulcer	1	-	-	2	1
Diverticulitis	-	-	1	-	-
Small bowel obstruction	2	-	3	4	-
Malabsorption	3	-	1	1	-
Urinary	-	-	-	-	-
Chronic cystitis	-	2	12	4	-
Bladder ulcer	3	1	2	1	-
Incontinence	1	-	1	-	-
Urethral stricture	2	-	1	-	-
Extensive cystocele	-	-	-	3	-
Others					
Vaginal stenosis	21	4	7	6	1
Vault necrosis	8	2	2	5	-
Postoperative pelvic abscess	1	-	1	2	-
Lymphocyst	-	-	2	2	-
Pulmonary embolus	-	-	1	-	-
Subcutaneous fibrosis	1	-	-	-	-
Leg edema	-	-	7	3	-
Hemorrhage	-	-	1	-	-
Thrombosis of pelvic blood vessels	-	1	-	-	-
Arteriosclerosis	1	-	8	2	-
Thrombophlebitis	-	-	1	-	-
Pelvic fibrosis	-	1	-	-	-
Acute pelvic cellulitis	-	1	-	-	-
Neuritis	-	-	-	1	-

Table 11: Late Complications of RT Alone (EBRT*+/- Brachytherapy) in Carcinoma Cervix N=1069

Toxicity	**5-year actuarial incidence (all grades)**	**Severe (RTOG Grade 3 & 4)**
Rectum	12.3%	1.1%
Bladder	11.2%	1.2%
Small Intestines	9.2%	0.2%
Subcutaneous tissue	23.1%	1.2%
Vaginal adhesions	29.6%	-
Vaginal Stenosis	33.9%	-

*External Beam Radiation Therapy

Table 12: Actuarial Complication Rate of Brachytherapy (Grade 3 or Higher) Correlated with Organ Site at 3 Years

	Overall (%)	**Genitourinary (%)**	**Rectum (%)**	**Small bowel (%)**
LDR* Brachytherapy	12	2.6	5.6	5.4
HDR** Brachytherapy	15	3.0	4.6	9.5

*Low Dose Rate

**High Dose Rate

Conclusion

All stages of carcinoma of the cervix can be cured or palliated by using radiation therapy. Whether with radical surgery or combined modality the treatment outcomes do not vary much, but the profile of acute and late toxicity differs. Urinary complication tends to be more in surgical patients while small bowel and rectal complications are more frequent in those who receive pre or post operative radiation therapy. The late complications with HDR brachytherapy are more than the LDR but with proper technique, optimization, separation (rectal and urinary bladder) and low dose more fractionated schedules, they are equivalent. Interstitial implant yielded better parametrial coverage and with fewer dose to rectal and bladder volumes. IMRT can be used to achieve lower bladder and rectal doses. IGBT is being rapidly adopted. With newer modalities like proton therapy, hadron therapy and inclusion of modern technological advancements in the radiation therapy planning, finding a cure for carcinoma of cervix with minimal complications is not too distant.

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