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Radiotherapy in Cervical Cancer

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ABSTRACT

Background: According to GLOBOCAN (2008), cervical cancer represents the first cause of cancer death in women in developing countries, the second most common neoplasia and the third most common cause of oncologic death. The present study aims to establish the impact of radiotherapy in patients with cervical cancer with regard to oncologic results and treatment-related toxicity.

Methods: A systematic literature review was performed based on database search in Cochrane Central Register of Controlled Trials (CENTRAL), the Cochrane Gynaecological Cancer Group Trials Register, MEDLINE, EMBASE, and included articles up to December 2015.

Results: Radiotherapy is used in IA to IB1 to those who refuse surgery or in inoperable cases. In stages IB2 and IIA both chemo-Radiotherapy and radical surgery, followed by adjuvant Radiotherapy with or without chemotherapy can be used. In stages IB2 to IVA, RT is used in a curative setting. In stage IVB palliative RT can only migliorate the quality of life and offer relief in presence of symptoms.

Conclusion: Newer Radiotherapy techniques can contribute to a significant reduction of acute and late toxicity to the organs at risk and can also offer a better target coverage, homogeneity and conformity. As accurate target volume delineation is important for Radiotherapy delivery, guidelines and multi-centre collaboration are essential.

Keywords: Radiotherapy, Cervical cancer, Effectiveness, Complications

INTRODUCTION

Cervical cancer represents a significant health problem worldwide and radiotherapy (RT) is one of the main treatment modalities. Several large prospective randomized clinical trials have shown that RT prolongs the disease-free survival (DFS) and reduces mortality. At the same time, a rapid development of the RT devices and techniques has been achieved. This combination improved therapeutic ratio of cervical cancer patients and reduced the incidence of post-radiation sequelae.

The purpose of this study is to assess the role of RT in cervical cancer patients in terms of oncologic results and treatment-related early and chronic toxicities.

MATERIALS AND METHODS

A review of all published reports in English language regarding RT for cervical cancer patients was performed based on data from Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Gynaecological Cancer Group Trials Register, MEDLINE and EMBASE. Articles up to December 2015 were included. The terms used for the search were “cervical cancer”, “radiotherapy”, and “irradiation” combined with one or more of the following: “toxicity”, “radiation-induced complications” and synonyms. Additionally, these terms were combined with the respective key words for each paragraph.

RESULTS

The treatment of cervical cancer is determined by the stage of the disease. Surgery is the standard therapy for early disease (FIGO stages IA, IB1 and selected IIA1). Microinvasive carcinoma FIGO stage IA1 is usually cured by more conservative surgical treatments such as cone biopsy, trachelectomy or simple hysterectomy [1]. Also patients with FIGO stages IA2 and IB1 (with tumor size <2cm) can undergo conservative treatment. In all these cases laparoscopic pelvic lymphadenectomy can be added in evidence of lymphovascular space invasion (LVSI). External Beam Radiotherapy (EBRT) is used in IA to IB1 in those patients who refuse surgery or in inoperable cases for other medical reasons or co-morbidities (i.e. coronary disease). In some studies both radical surgery and RT were demonstrated to be equally effective with 5-year survival rates of 87% to 92% for patients with FIGO stage IB1 [2,3]. The mainstay of treatment for advanced disease is either surgery followed by adjuvant RT with or without concurrent cisplatin chemotherapy or radical concurrent chemo-RT for inoperable cases [1,4,5]. Actually the optimal

management of stages IB2 and IIA remains debatable because both, primary chemo-RT and primary radical surgery followed by adjuvant RT with or without chemotherapy are effective [2,3,6]. In base of the results provided by five recent clinical trials NCCN guidelines recommend chemo-RT as primary treatment of choice for patients with FIGO stages IB2 to IV disease [7,8]. Thus, in stages IB2 to IVA, chemo-RT is used in a curative setting. In stage IVB palliative RT can be very useful relieving the patient from pain, bleeding, obstruction or extrinsic compression. In the curative setting RT is administered with a combination of EBRT and brachytherapy (BT). EBRT typically precedes BT because BT may be better optimized after potential maximal tumor shrinkage.

It is important to deliver RT doses to the primary tumor or to the tumor bed, in order to maximize the local control. In the treatment plan EBRT covers the whole pelvis and includes the primary cervical tumor, any parametrial, uterine, utero-sacral and vaginal extension. In post-operative patients the RT field includes the tumor bed, the vagina and the parametrial tissue. In locally advanced disease a combination of EBRT and intracavitary BT of cervix, vagina, and medial parametria must be given.

EBRT should also be delivered to the pelvic lymph nodes to eradicate microscopic and macroscopic nodal involvement and increase the regional tumor control probability. The pelvic lymph nodes that should be covered are the following internal, external, common iliac nodes and in selected cases the para-aortic nodes. When the tumor involves the distal half of the vagina, the inguinal lymph nodes must also be treated.

For the RT simulation, patients may be in the supine or in the prone position. The combination of prone positioning with the use of belly board can spare a large volume of small bowel. It can be very important in women who had a hysterectomy, because bowel may drop into the pelvic area. Wire markers over surgical scars can help to avoid the disease spread because of the surgical maneuvers. With the use of computed tomography (CT) the target RT volumes and the normal-tissue structures can be contoured. CT planning permits better assessment of the neoplasia or tumor bed, para-aortic and pelvic nodes. Due to the lack of visible soft-tissue detail of CT, a MRI-fusion procedure may be useful.

The superior RT field should be approximately at the level of the L4-5 interspace in order to treat the common iliac nodes. For patients with para-aortic nodal involvement, the superior border covers the renal hilum, usually at the T12-L1 interspace. The inferior border covers at least the obturator foramen unless there is distal vaginal or inguinal node involvement. When there is vaginal involvement, a fiducial marker or radiopaque clip must be positionated to the distal tumor extension because the entire organ should be irradiated. In both radical and adjuvant setting, the lateral field borders are 1.5 to 2 cm from the pelvic brim. The anterior border on the lateral field should be in front of the pubic symphysis, in order to cover the external iliac lymph nodes. For the para-aortic RT field, the anterior border rests approximately 2 cm in front of the vertebral body

or enlarged nodes. The posterior border must cover the entire sacrum which is covered because the uterosacral ligaments that insert onto the sacrum are at high risk of microscopic spread. For the paraaortic field the posterior border bisects the mid-vertebral body.

Radiotherapy Toxicity

Irradiation of a cervical cancer can cause functional disorders on adjacent organs such as small bowel, rectum, anus, bone, bone marrow, bladder, urethra, ureter, vulva, vagina and ovaries [9]. Patient's age, surgical procedure, radiation dose, tumor stage and medical co-morbidities (e.g. coronary disease, diabetes, collagenopathies) can impair the vascular supply of normal tissues and aggravate the RT-induced complications.

Gastointestinal Complications - GI (Small Bowel-Rectum-Anus)

In patients with para-aortic nodal metastasis, the use of extended field radiation therapy (EFRT) can be associated with a higher incidence of acute and late GI toxicity. Early injury at cellular level is characterized by loss of epithelial mucosal cells, endothelial edema of the arterioles, ischemia, acute inflammation and formation of eosinophilic crypt abscesses, decreased mitotic rate of the crypt cells within the mucosa [10,11] lamina propria's thickening, fibroblastic proliferation and fibrin–platelet thrombi accumulation [12] and secretion of cytokines (TNF-α, β).

Symptoms usually begin following 20 Gy of standard fractionation (1.8-2 Gy per fraction). Following completion of radiation, resolution of symptoms is seen in 2–3 weeks. Early symptoms usually include diarrhea, nausea, vomiting, pain, proctitis, tenesmus, bleeding and anemia. The delayed colorectal injury is a result of fibrosis of connective tissue and arteriolar endarteritis which leads to ischemia, friable vessels, telangiectasia, ulceration, fistula [13]. Late symptoms include urgency, painless bleeding, frequency, ulcers, strictures, fistulae and chronic diarrhea, fecal incontinence [14,15].

Genito-Urinary Complications (Bladder, Urethra, Ureters

The ureters, urinary bladder, urethra are covered by urothelium—mucosa made of transitional epithelium. Following radiation treatment, the injury is urothelial cell enlargement, multinucleation, vacuolization, loss of epithelial cells, loss of bladder impermeability, injury of stroma and blood vessels that produce hemorrhage and fibrin deposits [16,17].

The acute symptoms include frequency and dysuria and occur following more than 20 Gy with conventional fractionation. The late symptoms include persistent dysuria, pain, contracted bladder, stenosis, fistula, hematuria and hemorrhagic cystitis [18-20].

Lymphedema

In patients who have both surgery and RT the incidence of lymphedema is increased [21] Radiation produces cellulitis, thickening of the fibrous capsule and a decrease in the number of lymphocytes [22]. Lymphedema may be unilateral or bilateral.

Skin-Vulva

RT causes endothelial injury and vascular occlusions. It induces to early RT effects as erythema, dermatitis, edema, and late effects as loss of vulvar hair, depigmentation, fibrosis, telangiectasia and atrophy [23].

Vagina

RT induces endothelial injury of the squamous vaginal epithelium and it leads to acute effects as thrombosis, edema, and vaginitis. Delayed complications involve fibrosis, dryness, shortening, stenosis, dyspareunia [24], fistula formation, telangiectasia, chronic bleeding and ulceration [25-30].

Ovaries

RT induces to failure of ovarian estrogen production because of the damage of oocytes and proliferating granulose cells [31-33].

Early RT effects include endothelial edema and formation of vascular thrombi. Late RT injuries include arteriolar and venular fibrosis and atrophy.

Pelvic Bone Complications

RT can damage osteoblasts, osteocytes, and osteoclasts. The injury of the microvasculature compromises the periosteum blood supply and the osteoblastic function. The late osseous sequelae include horizontal and vertical fractures of sacrum and pubic bones, spontaneous femoral neck fracture and osteonecrosis [34-39]. Cigarette use and radiographic evidence of osteoporosis represent independent prognostic variables for increasing the toxicity risk. Both RT fractionation and amount of bone marrow included in the radiation field can affect acute and long-term myelotoxicity [40]. The combination of chemotherapy and RT can cause cumulative charge on hemopoiesis bringing to additional hematological toxicity. Prevention of myelotoxicity can be obtained using modern bone marrow-sparing RT techniques, particularly in these cases in which the iliac crests are included in the treatment field [41].

Newer techniques such as Three-Dimensional Conformal RT (3DC-RT), Intensity Modulated RT (IMRT), Image Guided RT (IGRT), Intensity-Modulated Radiotherapy with photons (IMRT), Volumetric-Modulated Arc Therapy (V-MAT), Helical Tomotherapy and Intensity-Modulated Proton Therapy (IMPT) [42-49] can contribute to a significant reduction of acute and late toxicity to the organs at risk (OARs) most notably the small and large bowel and the kidneys. Proton therapy such as passive scattered and IMPT, with its characteristic Bragg peak can obtain a significant reduction of complications to OARs [42,50,51]. Modern techniques can also offer a better target coverage, homogeneity and conformity.

Accurate target volume delineation is essential for RT delivery, because significant intra and inter-observer variability in clinical target volume (CTV) contouring may occur [52,53]. Education,

guidelines and multi-centre collaboration are needed to ensure inter-observer consistency in cervical cancer delineation and treatment planning [54-57].

CONFLICTS OF INTEREST

All Authors state they have no financial or other conflicts of interest that might bias the present work.

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