International Journal of Gynecology & Obstetrics 119S2 (2012) S155–S159

Contents lists available at SciVerse ScienceDirect

International Journal of Gynecology and Obstetrics

journal homepage: www.elsevier.com/locate/ijgo

FIGO CANCER REPORT 2012

Principles of radiation therapy in low-resource and well-developed settings, with particular reference to cervical cancer

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1. Introduction

Gynecologic malignancies may be treated either alone or with a combination of surgery, chemotherapy, or radiotherapy. Surgery and/or radiation are the primary treatment modalities used to treat cancers of the lower genital tract (vulva, vagina, and cervix). Primary radiation may be appropriate for all cancers of all 3 organs or radiation may be given as adjuvant treatment or in a palliative care setting [1,2].

2. Radiation treatment and dose–response relationships

The aim of radiation therapy is to achieve maximum tumor kill while limiting injury to the normal surrounding tissues. Solid tumors have a variable fraction of clonogenic cells that have the property to divide and proliferate like any other normal tissues in the body. All clonogenic tumor cells must be eradicated to achieve a cure. To improve the chances of cure, radiation doses may have to be increased, which results in increased acute reactions that may be acceptable to a certain degree. However, it is the risk of late reactions to radiation that needs to be reduced to minimize long-term morbidity in the surviving patient. The majority of adverse effects arise secondary to radiation damage to pelvic organs, such as the rectosigmoid colon, bladder, small bowel, femoral heads, and bone marrow. These can be minimized provided there is some understanding of the various radiation tolerances of different tissues.

2.1. Radiation tolerance doses

The tolerance of the cervix and uterus to radiation is usually more than 200 Gy. With these doses, the rate of necrosis is less than 1%. Tolerance doses of the upper vagina and surface of the distal vagina are less at 140 Gy and 100 Gy, respectively. Threshold doses reported for vesicovaginal fistula and rectovaginal fistula are 150 Gy and 80 Gy, respectively. The radiation-induced adverse effects and their manifestations depend on the type of tissues receiving radiation, i.e. early or late responding normal tissues and the radiation tolerances. Early responding tissues such as the skin and intestinal mucosa have a high cell turnover rate and they express radiation injury earlier, at about 2–3 weeks. Conversely, late responding tissues such as the spinal cord, rectum, bladder, and kidneys have a slow cell turnover or are nonproliferating, thus expressing radiation injury many years after treatment.

3. Radical radiation therapy for cervical cancer

A combination of external-beam pelvic irradiation covering the uterus, parametria, and pelvic nodes is followed by intracavitary irradiation. The aim is to deliver a dose equivalent to 80 Gy (biological effective dose BED = 2 Gy) to point A. The planned radical radiation/concomitant chemoradiation should be completed within 8 weeks. Prolonging overall treatment time results in poorer outcomes [3]. **Level of Evidence C**

3.1. External radiation

Using conventional fractionation, a dose of 40–50 Gy in 20–25 fractions over a period of 4–5 weeks is recommended. Using a 2-field or 4-field beam arrangement and corner shields helps reduce the dose to the rectum, bladder, and small bowel, thereby reducing the toxicities.

3.1.1. Radiation planning

Conventional planning is fluoroscopy-guided with the patient in the supine position. Under fluoroscopy guidance, bony landmarks are used to mark the portals. The upper border of the pelvic treatment portal is located at the L4–5 or L5-S1 interspace. The lower extent of the pelvic field is located at the midpubis or inferior border of the obturator foramina or to a line 4 cm below the lowest vaginal disease. Radio-opaque markers may be placed in the vaginal cavity to identify the disease on the cervix or vagina. The fields may be extended superiorly if there is suspected microscopic or gross metastatic disease in the para-aortic nodes. The lateral borders of the pelvic field are placed at least 1.5–2.0 cm lateral to the bony pelvic brim (bony pelvic sidewall). To compensate for patient movement in obese patients during treatment, the width of treatment field could be kept larger and corner shielding reduced.

In the 4-field technique (anteroposterior and bilateral portals), the anterior border of the field should be 1 cm anterior to the pubis to adequately cover the tumor and the anterior extent of the external iliac group of nodes with margins. The posterior border should be at the S3 vertebra to include the first two sacral vertebrae, which enables inclusion of the presacral nodes and uterosacral ligaments in the radiation field. Customized blocks to shield the small bowel region anterosuperiorly and the low anorectum region on the lateral fields are helpful in reducing late radiation toxicities. Additionally, inguinal nodes should be included if the disease is extending into/beyond the lower third of the vagina.

3.2. Intracavitary brachytherapy

Brachytherapy plays a very important role in curing cervical cancer. An accurately placed intracavitary insertion delivers radiation dose to the cervix, upper vagina, and medial parametria without exceeding the radiation tolerance doses to the rectum and bladder. Randomized trials comparing low-dose-rate (LDR) with high-dose-rate (HDR) brachytherapy in cervical cancer have shown that the two modalities are comparable in terms of local control and survival [4–7]. Either LDR or HDR brachytherapy can be used, taking into account the availability of equipment and other logistics of treatment delivery. HDR brachytherapy can be performed as a day procedure, in contrast to approximately 15–20 hours of continuous LDR treatment that requires overnight hospital stay as an inpatient. However, because of radiobiological considerations for minimizing late effects, 3–5 applications of HDR are required compared with 1–2 applications of LDR. With the increasing use of HDR treatments reporting fewer complications and better local control, and declining technical support for LDR, HDR is becoming a preferred brachytherapy technique. **Level of Evidence A**

For early-stage disease, the recommended brachytherapy schedules are either LDR 1–2 fractions of 25–30 Gy to point A, each 1 week apart, or HDR 3–5 fractions of 6–7.5 Gy to point A, each once weekly.

3.3. Concurrent chemoradiation with cisplatin chemotherapy

Five randomized Phase III trials of radical radiotherapy alone versus concurrent cisplatin-based chemotherapy and radiotherapy for the treatment of cervical cancer, and meta-analyses, have shown an absolute benefit in overall survival and progression-free survival with chemoradiotherapy in patients with Stage IB2 to IVA disease, as well as high-risk patients after hysterectomy [8–15]. While these trials vary somewhat in terms of heterogeneity in data, stage of disease, suboptimal doses of radiation, non-uniform usage of chemotherapeutic drugs, and different schedules and doses of cisplatin, they demonstrated a significant survival benefit for this combined approach. However, a Canadian trial [16] did not find any additional survival benefit of concurrent weekly cisplatin. The major criticism of the Canadian study was that nearly two-thirds of the patients who received chemoradiation had low hemoglobin, which was not corrected during radiation and this may have had a negative impact on the therapeutic outcome. Subsequently, an individual patient data-based Cochrane meta-analysis has shown that there was a significant improvement in the overall survival across all stages, although the magnitude of benefit was less in lower stages compared with higher stages. This analysis also showed a trend toward better outcome in patients receiving adjuvant chemotherapy following concomitant chemoradiation [17].

While chemoradiation is regarded as the new standard of care for women with cervical cancer, it is worth remembering that these results were obtained in a trial setting in women from affluent countries who had better nutritional or performance status and generally normal renal functions compared with the majority of women from lower socioeconomic countries. Women from low-income countries generally present with significantly more advanced disease, with poorer performance status, and may not tolerate combination therapy as well as women in better general health. Therefore, for women with medical or social reasons for doubtful compliance or poor tolerance to combined modality treatment, radical radiotherapy alone should be considered.

3.4. Therapeutic options for local relapse after primary surgery

Relapse in the pelvis following primary surgery may be treated by either radical radiation or pelvic exenteration. Radical irradiation (with or without concurrent chemotherapy) may cure a substantial proportion of patients with isolated pelvic failure after primary surgery. Radiation dose and volume should be tailored to the extent of disease. A dose of 45–50.4 Gy in 1.8–2.0 Gy fractionation should be delivered to microscopic disease followed by further boost to the gross tumor volume with external radiation to a dose of 64–66 Gy. If using concurrent cisplatin with radiation, including boost, total dose should be limited to 54–61.2 Gy. Where disease is metastatic or recurrent in the pelvis after failure of primary radiotherapy, a trial of chemotherapy with palliative intent for symptomatic control is indicated. Cisplatin and sometimes carboplatin with paclitaxel is used. The expected median time to progression or death in such patients is 3–7 months.

3.5. Local recurrence after primary radiotherapy

The only potentially curative treatment of local failure after primary irradiation is pelvic exenteration. Successful salvage is possible where central recurrences involve the bladder and/or rectum without evidence of intraperitoneal or extra pelvic spread and those who have tumor-free space along the pelvic sidewall. The triad of unilateral leg edema, sciatic pain, and ureteral obstruction is indicative of the extension of disease to the pelvic sidewall and, as such, is unresectable disease. This surgery should be undertaken only in centers with facilities and expertise available for this surgery and only by teams who have the experience and commitment to look after the long-term rehabilitation needs of these patients. The prognosis of recurrent disease is better for patients with a disease-free interval of greater than 6 months and recurrence 3 cm or less in diameter without extension to the sidewall. Following proper selection of patients, the 5-year survival with pelvic exenteration is in the order of 30%–60% and the operative mortality should be considerably less than 10%. In carefully selected patients with recurrent disease less than 2 cm and confined to the cervix and uterus, a radical hysterectomy may be performed. **Level of Evidence C**

3.6. Systemic chemotherapy in Stage IVB or recurrent metastatic disease

Chemotherapy has a palliative role in patients with metastatic or recurrent cervical cancer after failure of surgery or radiotherapy. There are a number of chemotherapeutic agents with activity in metastatic or recurrent cervical cancer. Cisplatin, at present, is considered the most active cytotoxic agent, with a response rate of 20%–30% and a median survival of 7 months. Although the older combination regimens failed to show an improvement in survival compared with cisplatin alone, the use of newer combinations has shown promise. In a Phase III Gynecologic Oncology Group (GOG) study, a combination of paclitaxel and cisplatin was superior to cisplatin alone in terms of response, progression-free survival, and sustained quality of life, but not for overall survival. In another GOG study, the combination of topotecan and cisplatin was superior to cisplatin alone for response, progression-free survival, and overall survival [18]. Therefore, selected patients with recurrent or metastatic disease in good general condition could be offered one of the newer combination regimens. For others, single agent cisplatin and best supportive care continue to be appropriate choices.

Distant metastases should be treated with a palliative intent with chemotherapy or radiotherapy or symptomatic and supportive care only. Local treatment with radiation therapy is indicated to sites of symptomatic involvement in patients with metastatic disease for alleviation of symptoms including pain arising from skeletal metastases, enlarged para-aortic or supraclavicular nodes, and symptoms associated with cerebral metastases. In view of the shortened life expectancy of patients with metastatic cervical

cancer, palliative radiotherapy should be given via larger fractions over shorter periods of time than conventional radical courses of treatment. Single fraction of palliative radiotherapy using 8–10 Gy or fractionated radiotherapy of 5 to 3 Gy in 4 to 10 fractions over 1 to 3 weeks will have good pain relief and adequate palliation of symptoms. **Level of Evidence A**

4. Treatment-related morbidity

Complications can be divided broadly into acute, subacute, and late. Acute complications manifest during treatment, subacute occur at 3–6 months, and late manifest after 6 months of treatment. These could be divided according to the principle treatment modality offered.

4.1. Radiation therapy

During pelvic radiotherapy, most patients experience mild fatigue and mild to moderate diarrhea that responds to antidiarrheal medications. Some women experience bladder irritation. These acute symptoms are increased when combined with concurrent chemotherapy or extended field radiation. Patients receiving concurrent chemotherapy may additionally have hematological and nephrotoxicity (cisplatin).

The late sequelae following radiation therapy commonly seen are due to the impact of radiation on rectal, bladder, and small bowel function. These depend on the duration of follow-up, type of treatment modalities, and estimated radiation doses to these organs. The reported grade III/IV late sequelae (toxicities requiring hospital admission or intervention) range from 5% to 15%.

Late rectal sequelae in the form of chronic tenesmus, telangiectasia and profuse bleeding, rectal ulceration, and strictures have been reported (5%–8%). These are usually seen during the 18–36-month follow-up period. The treatment options include steroid enemas, argon plasma coagulation, laser therapy, or formalin applied to affected mucosa, and in some instances, diversion colostomy.

Late bladder complications may occur in the form of continuous hematuria, necrosis, and rarely vesicovaginal or urethrovaginal fistula. The incidence of symptomatic grade III/IV late toxicities of the bladder after radical radiation is 4%–8%. Hyperbaric oxygen therapy (HBOT), though controversial, may be tried for the treatment of hematuria.

Late small bowel sequelae in the form of chronic enteritis, subacute intestinal obstruction, perforation and/or strictures may be encountered following a curative course of radiotherapy. The incidence of symptomatic grade III/IV late toxicities of small bowel after radical radiation is 3%–12%. These sequelae are higher in patients undergoing radical surgery especially transperitoneal pelvic lymphadenectomies followed by adjuvant radiation with or without chemotherapy (i.e. two major radical treatment modalities).

Most patients treated with radical radiotherapy have telangiectasia and fibrosis of the vagina, resulting in significant vaginal shortening, which may impact negatively on sexual satisfaction and ease of intercourse. These complications can be minimized by appropriate counseling and training in the use of estrogen cream with vaginal cylinders at the time of radiotherapy. Regular intercourse is likely to enable some stretch of the vagina and oil-based lubricants are advised rather than water-based lubricants.

5. Newer radiation techniques

In the past 10–15 years there has been rapid progress in radiation delivery techniques in parallel to advances in technology and imaging. Newer external radiation techniques, such as intensity modulated radiation therapy (IMRT), image-guided radiation therapy (IGRT), and PET-CT guided radiation, have also been explored in cervical cancers. However, these need further validation and at present there is no convincing evidence for their use.

An oncologist needs to contour (draw) the target volume and normal tissue so that radiation doses can be prescribed. The target includes gross tumor volume (GTV), which includes disease involving the cervix and extension to the parametrium, vaginal wall, uterus, and lymph nodes. Clinical target volume (CTV) includes the entire cervix, uterus, and parametrium up to the lateral pelvic wall and upper 2 cm of vagina below the lowermost gross involvement and lymphatics. Planning target volume (PTV) includes appropriate margins over the CTV. Recently, many authors have proposed guidelines to contour nodal/lymphatic CTV in cervical cancer [19–21]. Similar to identification of target volume, identification and contouring of normal tissue are vital because newer techniques such as IMRT can achieve optimal sparing of normal tissues without compromising the doses to target. However, the day-to-day organ motion during the course of radiotherapy remains potentially problematic. Various normal tissues contoured are bladder, rectum, sigmoid, small and large bowel, and bone marrow [22–24].

There are potential advantages with the use of IMRT over conventional 2D treatment, including the following:

- *Limiting doses to normal tissues*: This factor is of paramount importance and is going to be increasingly relevant in the future with the increasing intensity of treatments used routinely [22–25].
- *Dose escalation* to the central tumor is theoretically an important application of IMRT to any site. For cervical cancer, brachytherapy excludes most of such need. However, in locally advanced stages with inappropriate geometry and size for brachytherapy of residual disease, IMRT can be used [26,27].
- *Concomitant boost application* to special target regions can be achieved using IMRT. These regions may include pelvic or para-aortic lymph nodes or the lateral one-third of parametrium [19].
- *Prophylactic extended field radiation*: With increasing stage, the risk of para-aortic lymph node involvement increases and would befit prophylactic treatment. Conventional 2D treatments have long been criticized for increased bone marrow and bowel toxicity. However, with IMRT, doses of 50 Gy can be safely delivered to these regions [28,29].
- *Radical treatments for para-aortic lymph nodes*: Although FIGO staging does not change with identification of para-aortic lymph nodes identified in imaging alone, the treatment should. Recently, several authors have prescribed radical doses of 60–66 Gy with concurrent chemotherapy and demonstrated good local control and acceptable toxicities [25,28–30].

6. Advances in cervical brachytherapy

Historically, the brachytherapy systems such as Manchester, Paris, and Stockholm, derived from rich clinical experience, were used to deliver specified doses to the tumor in the absence of treatment planning systems. Later with the development of various manual and after-loaded applicators and different radium substitutes such as ^{137}Cs, ^{60}Co, and ^{192}Ir, the potential therapeutic impact of brachytherapy became evident. High-dose-rate remote after-loading and advances in treatment planning systems have ensured well-defined protocols and methods for brachytherapy dose analysis. However, the imaging modality used in brachytherapy was largely limited to 2D orthogonal radiographs. The major limitation of the conventional imaging modalities is applicator and point-based and there is a lack of information on the tumor volumes and organs at risk. Conventionally, point doses are calculated for the rectum and bladder according to International Commission on Radiation Units and Measurements (ICRU) Report 38 recommendations. However, point doses do not represent the

dose received by the entire volume of the organs, and therefore the doses to the organs at risk are not accurately known. This is evident from the lack of significant correlation between the point doses and incidence of toxicities, especially bladder and small bowel. In addition, the extent of residual tumor cannot be seen in the radiographs, hence the dose gradient across the tumor, especially in larger tumors, cannot be guaranteed.

Over the last two decades, various imaging modalities such as ultrasound, CT, MRI, and PET have been explored in an effort to delineate the tumor volume to be targeted by external beam radiotherapy (EBRT) and brachytherapy. Among the imaging modalities, MRI is becoming increasingly popular for diagnosis and treatment planning for EBRT and brachytherapy. Image-guided brachytherapy (IGBT) has been possible mainly because of MRI, where it is possible to image the applicator with tumor volume and other normal tissues. The American Brachytherapy Society (ABS) and Image Guided Brachytherapy Working Group (IGBWG) have provided guidelines in reporting IGBT that recommend the prescription of dose to a volume rather than a point. Later, the Groupe Européen de Curiethérapie and the European Society for Therapeutic Radiology and Oncology (GEC-ESTRO) published guidelines for reporting IGBT, which have been widely accepted. It is hoped that this will lead to a unified approach to reporting brachytherapy dosimetry [31]. According to these recommendations, the gross tumor volume encompasses T2 bright areas in the cervix; the high-risk clinical target volume (HR-CTV) encompasses the entire cervix and all visible or palpable disease at the time of brachytherapy; and the intermediate-risk volume (IR-CTV) is a 1-cm margin around HR-CTV with the initial sites of involvement. The IR-CTV includes vaginal extension at the time of diagnosis that may have been significantly decreased over time, and requires subtracting the normal tissues.

GEC-ESTRO also recommends starting with the standard method of dose prescription, either point A or the 60 Gy reference volume, and then adjusting the loading pattern and dwell times to ensure comprehensive target coverage. All patients should have the D90, D100, and V100 recorded for the high-risk CTV [32]. Currently, treatment of the full length of the tandem with some modification of only the top dwell position based on sigmoid dosage is recommended.

7. Current status of image-guided brachytherapy

One of the largest series published so far is from the Vienna group, which has reported the clinical outcome of 156 patients treated with image-guided adaptive brachytherapy combined with 3D conformal EBRT with or without chemotherapy [33]. The results are promising, with excellent local control rates of 95% at 3 years in limited/favorable (Stage IB/IIB) groups and 85% in large/poor response (Stage IIB/III/IV) groups with acceptable treatment-related morbidity rates. Compared with their historical series, there is relative reduction in pelvic recurrence by 65%–70% and reduction in major morbidity.

Other outcome data published from Paris and Mumbai endorse the same [34]. This is being tested further in an ongoing multicenter study involving several institutes in Europe, the USA, and Asia. (EMBRACE Study).

The potential of ultrasound as an alternate imaging modality for guidance of intracavitary brachytherapy for cervical cancer is also being explored [35,36]. The advantages of the universal availability of ultrasound, its cost-effectiveness, advances in 3D and real-time ultrasound imaging, and the small learning curve would make the application of this modality especially useful in low-resource countries.

Conflict of interest

The authors have no conflicts of interest to declare.

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