Chapter 12
Radiotherapy in Cervical Cancer

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Abstract Cervical Cancer is one of the most common types of cancer in the female Mexican population, and unfortunately, in almost half of all cases, the patient presents with locally advanced clinical stage, therefore being familiar with all radiotherapy techniques is crucial in order to give our patients the best possible outcome. Stage by stage the possibilities with radiotherapy treatment are so many: from conformal radiotherapy to the most modern techniques such as stereotaxic radiotherapy and IMRT are tools that we can use depending on the clinical scenario, and all those type of treatments are described and discussed in this chapter. What is the most important thing to remember is that every patient is a different case and we always have to individualize treatment to get best results.

Keywords Cervical cancer • Radiotherapy • Brachytherapy • Adjuvant radiotherapy • Point A • Intensity modulated radiotherapy

12.1 Early-Stage Cervical Cancer

Treatments for early-stage cervical cancer are mainly surgical because the control rate is high and the expected toxicity in surgery is low. When surgery is compared to radical radiotherapy, the data show that toxicity is lower after surgery than what is expected following radiation therapy. The main advantage of surgery over radiotherapy lies in the fact that it preserves the ovaries and sexual functions of young patients, which improves patient quality of life and avoids early menopause. We

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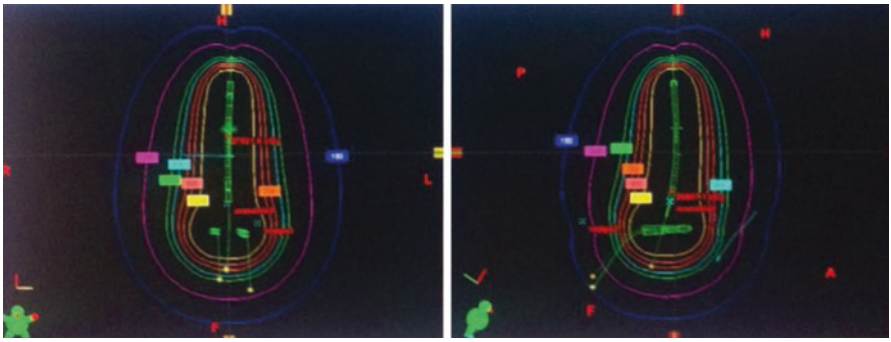

Fig. 12.1 Point A location. A pre-defined point that was located 2 cm above and 2 cm lateral to the external cervical orifice

cannot ignore the fact that morbidity is also lower and, finally, that the surgical procedure provides the surgeon with the possibility of obtaining a complete evaluation of the pelvis to identify implants or suspicious lesions outside of the cervix.

Studies have compared the results of surgery vs. radical radiotherapy in early stage cervical cancer. These studies have been mainly retrospective, and they have provided results that are comparable for local control and overall survival (OS) (80–90%) in a 5-year follow up [1].

However, this study showed that there were higher rates of toxicity in patients who were treated with radiation therapy. In 1997, the first randomized clinical study was published that compared radical radiotherapy to surgery. This study included patients with cervical cancer in stages IB-IIA. The patients were randomized to treatment with surgery or radiotherapy. In the surgical group, adjuvant radiotherapy was indicated for patients with a clinical stage above IIA, positive margins, positive lymph nodes or less than 3 mm of non-compromised cervical stromal tissue. External radiotherapy consisted of administering 47 Gy to the pelvic area followed by low-dose brachytherapy for a total dose of 76 Gy (point A). Point A was defined as a point located 2 cm above and 2 cm lateral to an external cervical orifice. This point represents where the ureter crosses the uterine artery (Fig. 12.1). There was no significant difference in OS (83 vs. 83%), progression-free survival (PFS) (74 vs. 74%) or local recurrence. The only difference was in the morbidity associated with the treatments: 28% of the patients in the surgical group received adjuvant radiotherapy, suggesting that the treatment choice should be based on the clinical stage, menopausal state, age, and, more importantly, cervical diameter to reduce complications secondary to treatment [2].

The treatment of choice for patients with early-stage cervical cancer is surgery, especially when the possibility of needing adjuvant radiation is low. In the opposite scenario, when adjuvant radiotherapy is thought to be required after surgery (e.g., because of large tumors, the risk of leaving residual tumors after surgery, of lymph node involvement) radical radiotherapy should instead be consider as a first option.

12.2 Adjuvant Radiotherapy for Cervical Cancer

As we discussed in a previous section, the treatment of choice for patients with early-stage cervical cancer in early stages is surgery. However, approximately one-third of the patients who going into surgery have one or more high risk factors for recurrence in their pathology report. The GOG-49 study [3] showed that having a tumor size larger than 4 cm, lympho-vascular invasion or invasion into more than one-third of the cervical stroma and exhibiting positive pelvic lymph nodes, positive surgical margins and parametrial involvement are predictive markers. In 1990, the GOG classified patients into the following three risk subgroups: low, intermediate and high-risk, with the latter having a 41% risk of recurrence.

To reduce this risk, postoperative radiotherapy treatments are recommended in the following two clinical situations: first, when there is an intermediate risk of recurrence, in which case, radiation therapy treatment alone is recommended (i.e., when lympho-vascular invasion is observed or the tumor size larger than 4 cm and involves more than one-third of stromal invasion); and second, when there is a high risk of recurrence, in which case, adjuvant treatment with chemo-radiotherapy is suggested (i.e. in the presence of positive pelvic lymph nodes, positive margins and positive parametrial invasion). In absence of macroscopic disease, a 45–50 Gy dose applied to the pelvis is typically prescribed as an adjuvant treatment. After external radiotherapy, the brachytherapy boost must be individualized. Once these factors were determined, several randomized trials that used adjuvant radiation to reduce local recurrence after surgery were performed.

In the first such trial, GOG-92 [4], the researchers analyzed results in patients with an intermediate risk of recurrence who received postoperative radiotherapy. The experimental group received 50.4 Gy of external radiotherapy to the pelvis. The control group was observed only after surgery. The results favored the treatment group, in which local recurrence was 14%, whereas it was 21% in the control group. As expected, higher toxicity was observed in the group that received radiotherapy (6% vs. 2.1%). An update after a 10 year follow-up confirmed that the patients who underwent external radiotherapy had a higher PFS (HR 0.58; p:0.009). However, no differences were found in OS [5].

The second randomized study, the GOG-109 study [6], included high risk patients. These patients were defined by the presence of positive parametrial invasion, positive margins or lymph node involvement. Patients were randomly assigned to receive either pelvic external radiotherapy at a total dose of 49.3 Gy (with 45 Gy to the para-aortic region whenever the iliac common nodes were positive) or chemo- and radiotherapy. The chemotherapy scheme was cisplatin- and 5-fluorouracyl-based. In this study, OS was higher in the group that received the combined treatment (71% vs 81%) after a 4-year follow-up, and the combined group also had a higher PFS (63% vs 80%). This information was confirmed in several trials after that publication [7].

The last randomized study to explore adjuvant therapy in cervical cancer was published in 2012 by the NOGGO-AGO Intergroup. Their study evaluated the use

of neo-adjuvant therapy in patients with a high risk of recurrence. A total of 271 of such CxCa patients were treated with either carboplatin and paclitaxel followed by radiotherapy or with standard chemo-radiotherapy. The study found that there was no significant difference in OS (86% vs 79%). They did demonstrate that the toxicity profile was different in every scheme, with nausea, vomit and hematologic toxicity displayed in the chemo-radiotherapy group and balding and neurotoxicity displayed in the group in which carboplatin and paclitaxel were sequentially administered [8].

It is reasonable to consider the use of brachytherapy in margin-positive patients [9]. In patients with broad residual disease, treatment with interstitial brachytherapy is the right choice. Furthermore, brachytherapy can be considered in cases where the parametrial tissue or the vagina has been compromised.

12.3 Irradiation Techniques

If a patient has early-stage cervical cancer (i.e. pre-invasive stages and up to 1A2) and refuses or cannot be taken into surgery because of a comorbidity, treatment with radiation therapy is feasible. However, in these cases, brachytherapy as a sole modality is preferred because the risk of lymph node involvement is low. The installation of brachytherapy devices is performed in the operation room, often while the patient is under sedation. The choice of device depends on the anatomy of the vagina (i.e., its size, length and compliance) and especially the target volume that needs to be covered.

There are several treatment schemes for brachytherapy. The choice should be based upon whether the treatment is going involve low dose rate (LDR) or high dose rate (HDR) brachytherapy. For LDR, the prescribed dose is approximately 65–75 Gy to the vaginal vault, and with HDR, the dose is 35–45 Gy and is given in fractions of 6–7 Gy. Using Manchester and GEC-ESTRO Systems, the treatment is administered at a 5 mm depth from the vaginal mucosa.

For patients with stages IB to IIA, the treatment consists of pelvic external radiotherapy and intracavitary brachytherapy with a prescription to point A. Two-dimensional treatment (2D) is based on predefined bone limits, which are localized using fluoroscopy. The tumor, uterus and pelvic lymph node tissue should be covered. The field's arrangement more commonly uses an anterior, posterior and two lateral (pelvic box) approaches. The superior border, which is determined based on bone anatomy, is delimited by L4-L5. This is the level at which the bifurcation of the aorta most commonly takes place. The lower border is marked by the inferior limit of the Obturator Foramen. The lateral border of the posterior and anterior fields is indicated by a line that is marked as an imaginary line 2 cm beyond the true pelvic ring. For the lateral fields, the anterior border is 1 cm beyond the pubic symphysis, and the posterior border is along an imaginary vertical line that is traced at the level of S2. The superior and lower borders of the lateral fields are the same as the ones for the anterior and posterior fields.

Three-dimensional radiotherapy treatment is based on anatomical limits according to the lymph node region and the extension of the tumor, which are observed on tomography. The region should cover the common, internal and external iliac lymph nodes and the pre-sacral lymph nodes, and the dose should be localized in the Obturator foramen. It also should cover the whole cervix, the uterus, the parametrial tissue that lies on the way from the cervix to the pelvic wall, the uterus-sacral ligaments and the upper half of the vagina. The peri-rectal lymph nodes should be covered if the pelvic lymph nodes are affected. Prophylactic radiation to the para-aortic lymph nodes is not routinely indicated unless these nodes appear to be affected. If that is the case, these nodes should be covered above the renal vessels, at approximately the T12-L1 level [10].

Brachytherapy should be administered during or after treatment with external radiotherapy. The protocol will depend on the preferences of the oncologic center, the patient's vaginal capacity, the grade of tumor regression and the concomitant use of chemotherapy. If the patient was not previously treated with surgery, treatment with brachytherapy should be performed using a uterine probe and ovoids (Tandem) to cover the entire cervix. If the patient no longer has a uterus, the treatment should be performed using a cylinder or ovoids, depending on anatomy and the volume that needs to be treated.

According to the Manchester System, which is evaluated by the ICRU 38, the dose should be administered to the A point. When using the GEC-ESTRO System, the dose should be targeted to the affected region regardless of pre-determined points of administration. This indicates that the residual tumor and the area presenting a high risk of recurrence should be covered. The final dose of radiotherapy to the A point or PTV (according to the type of brachytherapy) will depend on the clinical stage, which can vary from 65 to 75 Gy in stage IA1 and up to 85 Gy in stage IB and IIA [11].

12.4 Locally Advanced Cervical Cancer

Cervical Cancer is one of the most common types of cancer in the female Mexican population, and unfortunately, in almost half of all cases, the patient presents in a locally advanced clinical stage [12]. The reason for this is probably related to a lack of coverage by Pap-smear tests and, in many other cases, the fact that women tend to seek medical attention long after the appearance of the first symptoms. This results in the fact that surgical treatment can only be offered to a small percentage of presenting patients. The reason for this is that beginning with clinical stage IB2, treatment should preferably involve concomitant chemo-radiotherapy followed by brachytherapy. This protocol has already been described in several works, which have shown that there is an inverse relationship between size of the tumor and the probability of controlling the cancer. That is, the larger the tumor size, the less likely the treatment will be successful. This is because the effect of radiation depends on the amount of oxygen in the tissue. A large tumor generally has extended

areas of necrosis and decreased blood flow. This results in a compromised oxygen supply, which means that less oxidation damage is applied to malignant tissues. At the end of the 1990s, a series of publications changed the standard treatment for locally advanced cervical cancer patients, making concomitant chemo-radiotherapy the primary treatment option because it proved that it provided better results than when radiotherapy was used as the sole modality [14–17]. The fundamental idea behind the use of combined treatment is based on the synergistic effect between both modalities: chemotherapy acts as a radio-sensitizing agent that increases the tumor's susceptibility to the effects of radiation. This complicity between both treatments has several mechanisms of action, but it mainly inhibits the repair of sub-lethal damage and synchronizes cells in a particular radio-sensitive phase [18]. Also, the combined use of these treatments makes the effects of radiation less oxygen-dependent. The first concomitance studies were performed using hydroxyurea [14]. However, hematological toxicity was considerably high, and a randomized study was therefore carried out that compared the results of treatment with pelvic radiotherapy (at a mean dose of 50 Gy in conventional fractioning, i.e. 2 Gy) combined with the following three chemotherapy agents: cisplatin, fluorouracil and hydroxyurea or with hydroxyurea alone [13]. In all, 526 patients with stages IIB-IVA were included, and the results demonstrated that in both of the groups in which Cisplatin was administered, there was an improvement in OS and PFS, whereas more toxicity was observed in the group that received all three drugs than in the group that received cisplatin as the only drug. This is the reason why the standard treatment for locally advanced cervical cancer is currently radiotherapy plus cisplatin, with both treatments used concomitantly [13]. In a different study that was aimed at patients with a voluminous IB clinical stage, two groups were compared: patients that underwent hysterectomy after radiotherapy and those who were treated with chemo-radiotherapy. In this study, OS and PFS were better in the patients who were treated with the combined treatment (CT and RT) [16]. Finally, another study supported the superiority of treatment results gained using pelvic radiotherapy (50 Gy medium dose) combined with chemotherapy compared with pelvic and para-aortic region radiotherapy treatment without chemotherapy [15]. These results were confirmed in an updated publication on 2004 [19]. These studies are the basis for what is currently considered the standard treatment for locally advanced Cervical Cancer (Fig. 12.2).

Regarding the choice of treatment technique, several factors can be outlined. In patients with disease confined to the pelvic region (e.g., the cervix, pre-sacral region and high-risk lymph regions such as the iliac lymph nodes and obturator foramen), the four field technique can be used (e.g., AP-PA and opposing laterals) until 45–50 Gy is administered in conventional fractionations (e.g., 1.8 to 2 Gy per fraction), and in case of an enlarged lymph node (determined using imaging), these could be treated with a booster dose of 60–70 Gy. To achieve this high dose, we can use intensity-modulated radiotherapy (IMRT) because we need high dose gradients. In the absence of the availability of this technique, 3D conformal RT with medial-line

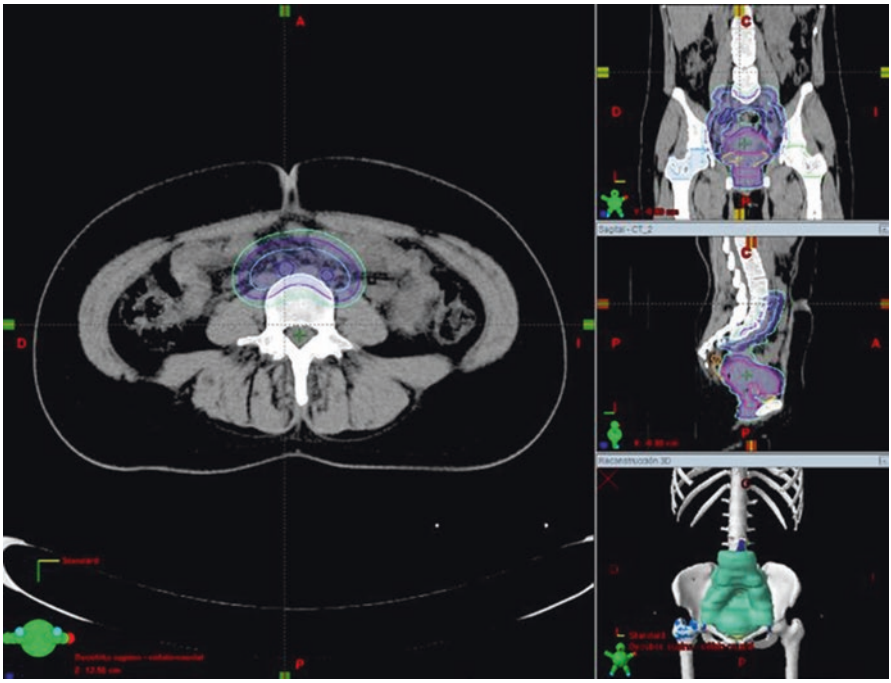

Fig. 12.2 Treatment volume in a patient with locally advanced cervical cancer. A contour has been drawn around the uterus, the cervix, the proximal one-third of the vagina, and the lymph node regions at risk (i.e., the iliac, presacrum and Obturator Foramen). In a head to tail orientation, the field extends traditionally from the bifurcation of the aorta (common iliac chain) to the point at which the tumor mass finishes with a 2 cm margin or down to Obturator Foramen. Lateral fields covered the region from the pubic symphysis to an imaginary line that was drawn at the level of S2. It is worth mentioning that these limits are the same that were used when planning with fluoroscopy (2D). Tomography is currently widely used to define treatment volumes

structure blockade (e.g., of the rectum, vagina and intestine) can also be performed [15]. It is worth mentioning that even though the availability of IMRT is increasing around the world, its use is not considered standard for this type of tumor because of the ongoing debate concerning factors that negatively affect local-regional control, such as how the target tissue is outlined, inter and intra-fraction movement, and tumoral regression during treatment [20–22]. Another alternative treatment that is increasingly accessible is stereotaxic radiotherapy (SBRT). This treatment consists of delivering high doses of radiation to a small target over a few sessions (generally no more than five). There are already reports of this technique being used on patients who are not candidates for brachytherapy after external radiotherapy. One of the largest series that has been performed reported highly motivating results in which no 3 or 4 toxicities were reported and satisfactory local control rates were achieved Fig. 12.3 [23].

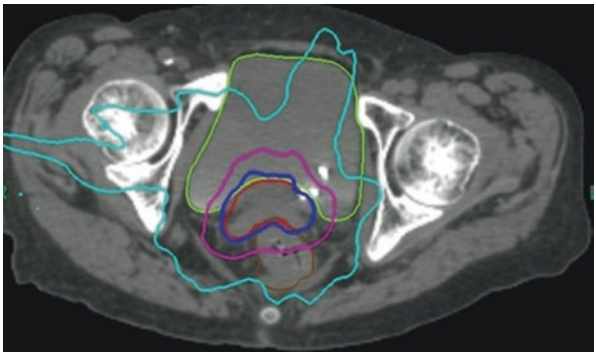

Fig. 12.3. Stereotactic radiation therapy after receiving conventional pelvic radiotherapy [23]

Table 12.1 The three risk stratification groups into which patients with cervical cancer were assigned

Low risk	Intermediate risk	High risk
Clinical stage IA and 1B1 patients with additional risk factors	Deep stromal invasion Lymphovascular invasion Tumor size >4 cm	Positive lymph nodes Positive margins Parametrial invasion
↓	↓	↓
No further treatment	Adjuvant radiotherapy	Adjuvant chemo-radiotherapy

Each group underwent surgical treatment. It was recommended that patients in the lower risk group did not need to receive any adjuvant treatment, whereas intermediate risk patients should receive adjuvant radiotherapy (tele-therapy and brachytherapy), and high-risk patients must be treated with adjuvant chemo- and radiotherapy (tele-therapy and brachytherapy)

12.5 Adjuvant Treatment in Locally Advanced Cervical Cancer

Approximately 80% of the cervical cancer cases in clinical stage I are cured by surgery and require no further treatment [24]. However, some well-known factors increase the risk of recurrence, thereby negatively impacting OS in these patients. The presence of positive lymph nodes is associated with a reduced 5-year survival rate [25]. A tumor size higher than >4 cm, deep invasion into the cervical stromal tissue and lympho-vascular invasion are all prognostic factors that increase the risk of recurrence and therefore affect LC and OS [26–29]. To achieve a more straight forward decision regarding whether a patient needs adjuvant therapy or not and whether this adjuvant treatment will be radiotherapy alone or radiotherapy concurrent with chemotherapy. A stratification risk has been develop to help the oncologist taking the decision. As shown in Table 12.1, low, intermediate and high risk of recurrence has been established.

In conclusion, approximately 20–25% of the patients that undergo surgery will possess an unfavorable prognostic factor that will dictate their need for adjuvant treatment. The adequate selection of such patients, both before and after surgery, is extremely important so that we can always offer the best treatment options according to the clinical and pathological characteristics of each patient. This allows us to guarantee the best possible oncological.

12.6 Brachytherapy

Radiotherapy has been successfully used in cervical cancer for approximately a century. Cervical tissues are particular sensitive to radiation. A combination consisting of external radiotherapy and brachytherapy has been shown to be an effective treatment option [30, 31]. Several studies have reported that brachytherapy as a boost after tele-therapy decreases the risk of recurrence and increases the survival rate. In selected cases, it may be used as the only component of a treatment scheme during the early stages of cervical cancer, and it is characterized by a close disposition between the radiation source and the tumor or vaginal vault [2]. The ICRU 38 defines the brachytherapy dose rates as follows: low dose rate (LDR) 0.4–2 Gy/hr., medium dose rate 2–12 Gy/hr. and high dose rate over 12 Gy/hr [32].

Low dose rate brachytherapy
This scheme has a long history as a treatment for cervical cancer. Initially, Radium 226 was used, but it was then replaced by Cesium 137, a radioisotope with similar physical characteristics, except that it has a lower half-life (30 years) than radium 226 (>1000 years) and results in health care providers being exposed to less radiation. According to ICRU 38, the permitted dose rate range for low dose brachytherapy is from 0.4 to 2 Gy/hr [33].

Pulsed dose brachytherapy
This is the most recent modality, and it was first used in San Francisco in 1992. It combines the physical advantages of a high dose rate and the radiobiological advantages of a low dose rate. It delivered radiation pulses in pre-established time intervals using Iridium 192 and the dose ranges described by the ICRU 28 are from 2 to 12 Gy/hr [34, 35].

High dose rate brachytherapy
This technique was first used on 1950, and the used of this treatment modality has increased considerably during recent decades. Currently, iridium 192 is used, and the ICRU 38 approves a dose from 12 Gy/hr. Among the advantages acquired with this kind of treatment in comparison with the low dose rate is that it avoids exposing the personnel in charge of patient care, allows dose optimization and higher reproducibility and is an ambulatory treatment. Several studies and meta-analyses found no difference in oncologic results or toxicity between the low dose and high dose rates [35]. Hence, independent of the absolute dose, the equivalent biological dose is the same for both modalities.

Applicators

Different applicator systems have been used to position the source of radiation inside the uterus and the vagina. These have included ovoids, a ring and a probe, a cylinder and a probe, and ovoids and a probe, but the most widely used ones are the Fletcher-Suit-Delclos.

The position of the applicators is a critical determinant. Conditions required for an adequate intracavitary insertion include:

1. The geometry of the insertion should avoid sub-dosification around the cervix.
2. The parametrial tissue most receive an adequate dose.
3. Doses to the vaginal mucosa, bladder and rectum should be monitored and maintained as the lowest possible level to decrease the risk of toxicity.

During the patient's initial evaluation, a determination is made regarding which applicators will be uses for the brachytherapy treatment, but the final evaluation will take place once external radiotherapy has concluded, and the ideal applicators will be selected based on the obtained response [34].

Planning of the treatment

Diverse methods have been used to determine the prescription points to be dosed during the evolution of brachytherapy. However, because of the limited availability of 3D images, most of the international instruction manuals continue to use orthogonal radiographies based on the definition of Point A and dose restrictions for the bladder (absolute <75 Gy, relative <90%) and rectum (absolute of 70% Gy and relative <80%). This was the nomenclature that was approved by ICRU 38 [36]. Fig. 12.4 shows treatment performed in tandem in patients with a uterus.

Dose

The American Brachytherapy Society (ABS) recognizes that the dose of external radiotherapy to the whole pelvis varies from one institution to another and that size of the dose and the number of fractions of a high dose rate of brachytherapy will depend on the doses given before in radiotherapy to the wholes pelvis. Some institutions limit the dose of external pelvic radiotherapy in early-stage patients to 20 Gy before performing the programmed brachytherapy. These institutions then complete the dose to the whole pelvis in a second round while using central protection. Nonetheless, most institutions prefer to first administer a 40–50 Gy dose of pelvic external radiotherapy and then lower the brachytherapy dose [37].

The optimal high dose rate brachytherapy scheme remains undefined, and the dose per fraction may vary by +/− 0.25 Gy. However, if goes higher than 7 Gy per fraction, then special care should be taken with the organs that are at risk (especially the rectum and bladder), given the long-term complications that exposure could present. It is also recommend that the length of treatment should not exceed 8 weeks to obtain the best results [34, 36]. The decision to use a higher dose in the external radiotherapy than in the brachytherapy will depend on the initial volume of the disease, the ability to separate the bladder and the rectum, the degree of tumor regression observed during external radiotherapy and the preference of the institution [37]. The most widely used dose schemes, each of which is recommended by the ABS, are listed below (Tables 12.2 and 12.3).

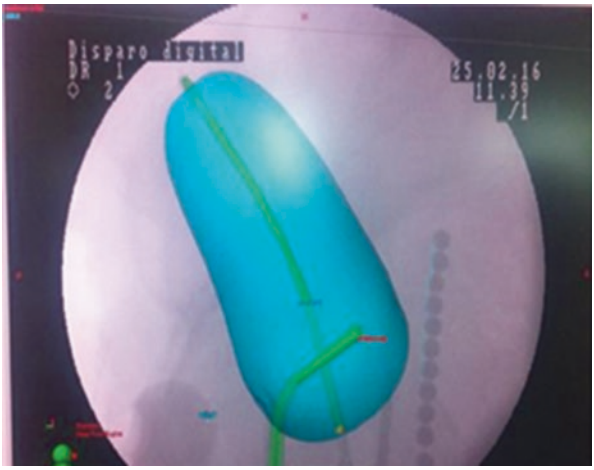

Fig. 12.4 Planning of a high dose rate brachytherapy treatment using a probe and ovoids. Note the position of the bladder (*left of the blue dose curve*) and rectal (*right to the blue dose curve*) probes. These two structures assist in defining the dose to give to the bladder and the rectal wall while determining dose tolerance limits

Table 12.2 Radiotherapy schemes recommended by the ABS to treat early-stage cervical cancer

External radiotherapy dose (Gy)	Number of fractions (brachytherapy)	Dose per fraction (brachytherapy)
20	6	7.5
20	7	6.5
20	8	6
45	5	6
45	6	5.3

Table 12.3 Radiotherapy schemes recommended by the ABS to treat locally advanced cervical cancer

External radiotherapy dose (Gy)	Number of fractions (brachytherapy)	Dose per fraction (brachytherapy)
45	5	6.5
45	6	5.8
50.4	4	7
50.4	5	6
50.4	6	5.3

Another gynecological brachytherapy planning technique is one that is guided by an image (3D). This is possible in both HDR and PDR. The localization of target structures is carried out using tomography, simulation and sometimes magnetic resonance imaging. The full GTV and CTV coverage is crucial and one of the most important prognosis factors that is directly related with the final results. Instead of choosing a prescription point, as in fluoroscopy panning methods, a prescription is

made to treat the volume involved, and dose restrictions for organs are made in association with the maximum prescribed dose (D2cc) [11].

The final dose of radiotherapy to point A or to the CTV (depending on the type of brachytherapy) will depend on the clinical stage and can vary from 65 to 75 Gy in stages IA1 and up to 85 Gy in locally advanced stages [11, 36].

12.7 Re-irradiation

It is estimated that approximately 35% of all patients with a cervical cancer diagnosis who are treated with radiotherapy will recur during the first 5 years after they finish treatment. In young patients with good status performance and small central recurrence, exenteration is the standard treatment. Complete resection (R0) significantly impacts the outcome of treatment. R1 resection, especially in tumors that are close to pelvic wall, can be treated with intra-operative radiotherapy [38]. However, the majority of patients with local recurrences after radiotherapy have an advanced age and severe comorbidities. For this reason, re-irradiation is often the preferred option in these patients. In fact, there are time when this is the only curative option. Whether external radiotherapy or brachytherapy is preferred generally depends on the conformal dose distribution offered by each technique, with the optimal strategy being the one with the possibility of delivering very high doses to the affected zone and smaller doses to surrounding tissues. There is currently not enough information available in the literature regarding the restriction of doses to at-risk organs 9, 10. In a previously published small retrospective series, a dose that included a total of +/− 48 Gy in conventional fractionation was found to be safe. This study reported disease-free survival and 5-year local control rates of 46 and 45%, respectively. Severe complications were reduced by the implementation of 3D planning for brachytherapy and IMRT. Nonetheless, there are adverse prognosis factors, such as a short period before recurrence (< 6 months) and a tumor size larger than 3 cm. It is very important to analyze the technique that was used previous to a recurrence (e.g., energy, volume, external radiotherapy dose and brachytherapy dose) and the time that has elapsed between treatments to determine the feasibility of re-irradiation [39].

High dose rate brachytherapy, rate can be applied either in intracavitary or interstitial form for re-irradiation but must be considered with extreme caution to reduce the potential complications.

Conclusions

Intra-cavitary brachytherapy is a very important part of treatments for cervical cancer, whether it is used as a sole modality or in combination with external beam radiotherapy. In multiple studies, a decrease in recurrence and an increase in survival have been reported when brachytherapy has been applied, given its capacity to deliver very high, localized doses while reducing the amount of radiation delivered to the surrounding tissues. This technique and dose fractionation schemes frequently vary between different institutions [38].

12.8 Toxicity and Complications Post-radiotherapy in Cervical Cancer

In 1999, the National Cancer Institute (NCI) announced that the concurrent use of chemotherapy and radiotherapy improved OS in locally advanced cervical cancer, and this treatment method was subsequently considered the standard treatment option. Pelvic radiotherapy plays a definitive roll in patients, but we cannot ignore the toxicity that is often associated with it. Because complications normally arise between 3–5 years after treatment, there is still much to investigate regarding long-term morbidity in this patients [40]. As radiation oncologists, we must be aware that even though our main concern and efforts are focused on controlling malignant cells, we must understand that the complications associated with these treatments can impact our patients' quality of life in a negative way.

The definitions of acute and late toxicity vary in the literature. In some cases, acute toxicity is defined as the presence of adverse effects that take place during treatment and up to 42, 60 and 90 days after radiotherapy is complete. Late toxicity refers to effects that present after 90 days or even years later. The incidence of late sequelae in patients with early-stage cervical cancer who were treated with radiotherapy is approximately 3.5%, whereas in patients with locally advanced disease, the rate of complications is reported to be slightly higher (10–15%). The reason for this difference is simple: the total dose to central structures tends to increase as the clinical stage of the patient increases (e.g., 85–90 Gy are administered to the cervix in clinical stage III and IV patients). We can conclude that the probability of complications arising is directly related to the clinical stage, the volume of tissue being treated, the patient's anatomy and the total dose administered to individual tissues [43].

Genitourinary toxicity

In cervical cancer, pelvic radiotherapy can result in complications in the lower urinary tract. Acute toxicity (G1–2) is relatively common following external beam radiotherapy (17–40%), depending on the report being described [41]. The risk of developing adverse urinary effects (e.g., grade 3 or 4) is higher in the first 3 years but has an actuarial risk of 0.25% per year for the next 25 years 44, and the annual incidence increases between 18 and 28% after 3 and 5 years post-radiotherapy, respectively [42].

It is estimated that 44% of these patients will develop adverse acute urinary effects (<9 days post-radiotherapy), while only 7–9.5% will develop adverse late effects44. However, the time required for these adverse effects to manifest can be substantial. For instance, the presence of urethral stenosis and spontaneous bladder rupture have been observed up to 30 years after radiotherapy is complete. From a physio-pathological point of view, this technique results in damage to the basal membranes of blood vessels, which can lead to occlusion, thrombosis, neovascularization and an increase in the proliferation of fibroblasts [44]. These events can subsequently lead to lesions in the urinary tract, with the bladder and the point

at which the ureter inserts into bladder being the most susceptible to damage, given their anatomical positions. Neo-vascularization is an important factor that contributes to radiation cystitis and the later development of hemorrhagic cystitis. The most common urinary adverse effects (grade three or higher) are urethral stenosis, vesicle-vaginal fistula, ureter-arterial fistula and hemorrhagic cystitis [43]. The risk of severe toxicity after radiotherapy is significantly associated with higher radiotherapy doses and the number of administered treatments [43, 44]. Urethral stenosis has been reported in 5% of pre-operative radiotherapy patients and in 25% of patients treated with definitive radiotherapy alone.

Gastrointestinal toxicity

Acute gastrointestinal toxicity can appear up to 90 days after radiotherapy treatment and is characterized mainly by diarrhea, tenesmus, and pain or hemorrhoids with rectal bleeding that can be controlled with symptomatic medication. Late toxicity could appear during the first 2 years or more after radiotherapy and is characterized mainly by proctitis, stenosis and rectal fistula.

Several risk factors can increase the chances of a patient experiencing toxicity due to radiation. Prior abdominal or pelvic surgery can increase the risk of intestinal obstruction or adherence formation in patients treated with radiation therapy (> 50 Gy). Additionally, patients with coexisting comorbidities, including previous pelvic inflammatory disease, atherosclerosis, diabetes, vascular disease, collagen disease, tobacco consumption history or intestinal inflammatory disease, might have an increased risk of developing acute or long-term secondary effects following radiation therapy [45].

Eifel et al. [43] reported increase in toxicity and a higher risk of chronic adverse effects in patients with cervical cancer who were treated with radiotherapy. The risk was higher during the first 3 years of treatment, with 7.7% of patients presenting with G3 complications within 3 years. The incidence of rectal complications was 1% during the first 2 years and lowered to 0.68% from 2 to 25 years. The incidence of fistula was approximately twice as high in patients who were subjected to extrafascial hysterectomy and adjuvant treatment. These patients presented with this complication at rates of 5.3% and 2.3%, respectively, at 20 years post-radiation, and 5.2% and 2.9%, respectively, in patients who were previously subjected to laparotomy. The risk of intestinal obstruction is also increased in patients subjected to laparotomy (14.5% and 3.7%, respectively, after 10 years), and patients who weighted <120 lb. (8.2% and 3.6%, respectively). The cumulative risk of complications was higher in young patients because they had a stronger probability of survival and were therefore exposed for a longer period of time.

Mitchel et al. [46] evaluated 398 patients with clinical stage I-III cervical cancer who were treated with definitive radiotherapy. The patients were divided into two groups, as follows: those who were 35–69 years old and those who were >70 years old. The frequency and severity of acute and late adverse effects were equivalent in both groups. Age was therefore not associated with higher rates of acute or chronic toxicity.

There is a direct correlation between the incidence of complications and the dose administered. Pérez et al. [47] reported that with doses <75–80 Gy the risk of G2–3

complications in the urinary tract and rectum is approximately 5%. However, this percentage increased >10% when higher doses of radiation were applied. In the small intestine, the incidence of morbidity was lower (2%) in patients treated with less than 50 Gy than in those treated with >50–60 Gy (5%). It has been demonstrated that patients who experienced treatment sequelae had slightly better survival rates than patients without complications. This result was associated with better tumor control when administering high doses of radiotherapy.

The effects of the total dose of radiotherapy on the bladder, rectum and point A are also correlated with the severity of the complications. Eiffel et al. evaluated 1456 patients who were treated with external radiotherapy and LDR brachytherapy consisting of a total dose of 70–90 Gy. The frequency of G2 morbidity in these patients was 10–12%, and the frequency of G3 morbidity was 10%. The most important adverse effects ere cystitis and proctitis (G2) (0.7–3%), vesicle-vaginal fistula (G3) (0.6–2%), rectal-vaginal fistula (0.8–3%) and intestinal obstruction (0.8–4%). In the bladder, doses <80 Gy were correlated with a <3% incidence of morbidity, and this incidence increased to 5% with higher doses. In the rectal wall, the incidence of morbidity was <4% when <75 Gy was applied. In the small intestine, the incidence of morbidity was <1% when 50 Gy or less was administered, 2% for 50–60 Gy and 5% for higher doses [48].

There are a variety of dosimetry parameters that are tightly correlated with the incidence of morbidity in patients who were treated with definitive radiotherapy. Hence, we should pay special care and attention to these related factors, which will help us reduce morbidity to a minimum without compromising tumor control.

The correlation between tobacco and late complications following radiotherapy is of particularly interest. A significant difference has been observed in the incidence of intestinal complications between smokers and non-smokers, and this difference was associated with the intensity of tobacco consumption. These data provide evidence regarding a synergistic effect between tobacco use and the effects of normal tissue radiation [13].

Sexual function after pelvic radiotherapy

The most common gynecological complications following radiotherapy are ovarian insufficiency in pre-menopause patients and vaginal stenosis in patients that receive vaginal radiation. Vaginal stenosis is defined as a tightening or reduction of the vaginal canal that can interfere with a physical exam or sexual function. Its incidence varies between 20 and 88%. In patients who are initially subjected to surgery and then later receive vaginal HDR brachytherapy, the incidence is lower 2.5% [16]. It is most common for this complication to occur during the first year post-radiotherapy, but it has been observed at intervals ranging from 26 days up to 5.5 years. The risk factors associated with vaginal stenosis include high doses of radiation, patients who are >50 years old, insufficient use of the dilator, and concomitant chemoradiotherapy. Doses >80 Gy have been associated with a 10–15% increase in the risk of G2 vaginal toxicity, including vaginal stenosis [49]. Radiation-induced menopause generally occurs within 6 months after treatment.

Hematologic toxicity
High doses of radiation can induce chronic myelo-suppressive effects and lower tolerance to chemotherapy by damaging the bone marrow micro-environment. The results of prospective studies have reported a 25% incidence of hematological toxicity >G3 when using cisplatinum-based chemo-radiotherapy. Irradiating an extended field that includes the covering over the para-aortic lymph nodes results in more irradiation of total bone marrow and therefore a higher rate of hematological toxicity. It is important to consider this complication and to monitor hematological toxicity because it predisposes patients to infections, frequent hospitalizations, multiple transfusions and delays in receiving chemotherapy [50, 51].

Brachytherapy toxicity
In a meta-analysis published by Cochrane in 2010, LDR and HDR intracavitary brachytherapy were compared in locally advanced cervical cancer. All of the included studies, which involved 1265 patients, provided detailed information regarding the complications that presented. The tissues found to be at risk of late complications were the bladder, sigmoid rectum and small intestine. The relative risk for late complications was 1.33 in the bladder, 1.0 in the sigmoid rectum and 3.37 in the small intestine. These results indicate that except for a slight increase in the complications that presented in the small intestine, there were no significant difference in complication in patients treated with a high dose [31].

Complications of concomitant radiotherapy/chemotherapy
Concerning the recent application of chemo-radiotherapy, it has been clearly demonstrated that this combination results in higher rates of acute toxicity, particularly hematologic and gastrointestinal complications, than radiotherapy alone.

Kiran et al. [52] carried out a review of acute and late toxicology following chemo-radiotherapy in 1766 patients. They found that G1 and G2 hematologic toxicity effects occurred more often in the chemo-radiotherapy group. A significant difference was observed in G3 and G4 hematological and gastrointestinal toxicity. Late toxicity has been described in eight assays, seven of which reported a significant difference. However, the survival benefit obtained from applying chemo-radiotherapy makes up for the toxicity observed in these patients, and this makes this strategy an acceptable option.

In spite of the fact that there is not sufficient data on late toxicity to support its results, the data obtained from meta-analyses performed in the RTOG 900198 study [53, 54] suggests that there may not be any significant difference in the type or severity of the late effects produced by chemo-radiotherapy or radiotherapy alone. Only a small percentage of women (1–3%) presented with severe late toxicity, and these complication primarily affected the rectum, bladder, intestines and vagina.

New radiation techniques aim to improve toxicity
As new radiation techniques have been developed, it has now become possible to minimize or substantially prevent G1 toxicity. The use of multiple fields avoids a lack of homogeneity in drug dose delivery. Additionally, the physical displacement

of the intestines can be optimized by using a “belly board” while the patient lies in a prone position, and the procedure is now generally performed while the patient has a full bladder. Improved moderate radiotherapy treatment (IMRT) may contribute even further to reducing the rate of G1 toxicity. Moderate radiotherapy treatment is highly conformal and uses many angles to better adjust the treatment to the tumor’s geometry and minimize the dose applied to the normal surrounding tissues. The most recent technique, image-guided radiotherapy (IGRT), permits some adjustments during treatment and enables the practitioner to reduce the dose delivered to normal tissues by a higher percentage [55].

Ghandi et al. [56] published the results of a randomized study that evaluated toxicity and clinical results in 44 patients with locally advanced cervical cancer who received 3D pelvic radiotherapy vs IMRT with a dose of 50.4 Gy, which was delivered in 28 fractions that were administered concomitant with 40 mg/m2 cisplatin and followed by HDR intracavitary brachytherapy. IMRT was associated with a lower rate of acute G1, >G2 (63.3% vs 31.8%) and >G3 (27.3% vs 4.5%) toxicity in addition to a lower rate of late G1 toxicity (50 vs. 13.6%). In a dosimetric comparison between both groups, IMRT applied a significantly lower dose to the small intestine and rectum.

New techniques that involve 3D imaging, either with TAC or with IMR, help us to better delimit the form of the surrounding tissues in patients that receive a high dose of brachytherapy, which allows us to achieve reductions in toxicity.

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