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Interstitial Brachytherapy in Gynaecological Cancer
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1 Introduction

Interstitial brachytherapy is generally reserved for patients either with extensive pelvic and/or vaginal disease in an attempt to improve local control or with anatomy not allowing intracavitary brachytherapy with standard applicators. The aim of this technique is to tailor the dose of irradiation to the anatomy of the patient with a better target volume coverage. The technique was initially developed using radium 226 (1,2) (Fig 17.1) or cobalt 60 (3) needles. Originally, interstitial implants were performed with free-hand placement of the radioactive needles (4). The development of transperineal (5,6,7,8,9,10) or transvaginal (11,12) templates resulted in a better needle positioning. Newer techniques including fluoroscopy (13), computed tomography (14), transabdominal or transrectal ultrasound (15), magnetic resonance imaging (16), laparoscopy (17), and laparotomy (18) have improved the needle placement accuracy. Radioactive material consists of Iodine-125 seeds employed as permanent implants (19) or more generally Iridium-192 seeds or wires sources employed as temporary implants with either low dose rate or high dose rate. Despite an improvement in the technological approach of these techniques, the potential benefit of interstitial brachytherapy in gynecological malignancies has not been clearly demonstrated. This technique is associated with a potential increase in the risk of complications.

![Fig 17.1: Interstitial radium implant.](image)

2 Topographical Anatomy
3 Pathology
4 Work Up

See chapter 14-16 on cervix cancer, endometrial cancer and primary vaginal cancer.
Fig 17.2 Endosonography of vaginal recurrence
A: Vaginal relapse at the vaginal apex adjacent to the base of the bladder after radical surgery for endometrial cancer without postoperative adjuvant brachytherapy. Endosonography for treatment planning of interstitial brachytherapy. Dimensions and volume of the GTV: 4 cm wide, 3 cm thick and 3 cm long in transversal, sagittal and coronal view, volume was 20 cm$^3$.
B: Periurethral relapse with endosonography for planning of interstitial brachytherapy indicating the urethra and the tumour dimensions and topography 4.5 cm wide, 2 cm thick, 3 cm long. GTV was 14 cm$^3$.

5 Indications

Indications for interstitial brachytherapy in gynecological malignancies are represented by different clinical situations:

1. In patients with cervix cancer, interstitial brachytherapy is used when parametrial extent of the tumor cannot be encompassed by standard intracavitary brachytherapy. In a report on patterns of radiotherapy practice for patients with cervical carcinoma, Eifel et al (20) reported interstitial brachytherapy included in 35 (8%) of the 455 patients who had brachytherapy. This technique was used in 19% of the patients who presented Stage III disease treated with curative intent (20).

2. A second indication is a narrow vagina not allowing the use of appropriate vaginal applicators to arrive at a sufficient dose distribution due to poor geometric conditions.

3. A third indication is represented by patients who had prior hysterectomy with the impossibility of a tandem placement. The two former situations can be resolved with the use of a personalised applicator (5,6,7,8).

4. A fourth indication includes patients with a recurrence inside an area previously irradiated restricting the use of further external irradiation.

5. In patients with primary vaginal tumors, interstitial brachytherapy has been reported when paravaginal extension is not correctly encompassed with standard intracavitary brachytherapy (6,7,9,10).

6. Patients with vaginal recurrences, especially from endometrial cancer have been recognized as good candidates for interstitial brachytherapy techniques with potential sparing of bladder and
rectum. These techniques have been shown to improve dose distribution particularly for deeply infiltrating tumors (11,12)

6 Target Volume

See chapter 14-16 on cervix cancer, endometrial cancer and primary vaginal cancer.

7 Technique

Different templates were designed in order to get a better target volume coverage. Combination of intracavitary and interstitial brachytherapy is possible.

According to the tumour response after the first time of irradiation, brachytherapy can be realised in one or several sessions. The combination of these two kinds of brachytherapy is called the “Sandwich-Technique”, which allows to deliver a high dose to the tumour with sparing the healthy tissues.

Some of the described templates are transvaginal, others are transperineal. Different after-loading guide materials have been reported:

7.1 Guide gutters (5,6)

The guide gutters enable the implantation of hairpin sources composed of 0.5 mm iridium wires. Different lengths of 3, 4, and 5 cm are available.

The technique of implantation depends on the location and the extent of the tumour. Usually, this technique is used with transvaginal implantation.

For cervical tumours extending to the anterior vaginal wall or for primary vaginal cancer with an anterior vaginal extension, a Foley catheter is first inserted, as a guide for the gutter implantation. For posterior wall vaginal extension, one finger, introduced into the rectum, checks the relationship between the tumour and the position of the implants. In these cases, the implants are parallel to the axis of the vagina.

Fig 17.3: Sandwich technique: mould vaginal applicator combined with two guide gutters implant (transvaginal technique) in paravaginal tumoral extent.
In case of parametrial and/or paravaginal invasion, the guide gutter technique can be proposed. In that case, a large vaginal cavity is essential to perform a satisfactory application with implants perpendicular to the vaginal axis.

### 7.2 Plastic tubes (5,6)

Easily pliable, they fit better to large tumours but the application can be more difficult. Two techniques are available:

Loops and blind plastic tubes. In the first one, guides must be placed through vaginal route to achieve a loop. In the second one, the implants pass through the perineum which is technically easier. Moreover it represents an improvement in dose distribution to the parametrium. For both reasons this later method is generally preferred. In both techniques, plastic tubes are parallel to the vaginal cavity.

![Blind plastic tube implant (transperineal technique): tubes are parallel to the vaginal axis.](image)

In order to assure a fixation different devices are used: pre-perforated tubes, plastic plates and metallic buttons. These systems are more often sutured to the perineum skin.

### 7.3 Plastic needles

Plastic needles are constructed (like guide needles) as hollow needles consisting of stiff plastic material. They are available with an outer diameter of 1.6 - 2.0 mm and a variable length of 20 or 24 cm and can be obtained either with a round “sharp” end or a bevel shaped end. They are inserted with a stainless steel obturator which can be removed after placement. The steel obturator is visible under fluoroscopy and under ultrasound guidance. After removal of the obturator the needles can also be easily visualised on CT scans and on MRI without causing artifacts.

Plastic needles can in principle be used for every type of interstitial gynaecological brachytherapy as described for stainless steel guide needles, in the vagina, in paravaginal and parametrial tissues in form of a free hand technique or in combination with intravaginal and perineal templates. Compared to steel guide needles the disadvantage is that they more easily tend to slightly bend in very stiff tissues (see Fig 17.8 and 9).

### 7.4 Guide needles.

These needles are used with different types of templates:
7.4.1 Intravaginal templates

Charra et al (11) described a dedicated intravaginal template (Fig 17.5). This template is a Plexiglas parallequipped with two ranks of three canals, arranged as squares (Fig 17.5A). All the canals are parallel and separated by a distance of 10 or 12 mm. The depth of the canals inside the template was designed in order to have the reference isodose, according to the Paris system rules, at the level of the template surface.

The implantation is standardized and consists of six parallel metallic needles secondarily loaded with 192-Iridium wires of four to six cm length (Fig 17.5B). The needle extremity is beveled and blinded to avoid bleeding. When necessary, this intravaginal implant can be combined with a transperineal implant.

Similar intravaginal individually fabricated plastic applicators/templates of different diameters can be used carrying canals parallel to the axis of the vagina in a fixed geometry, e.g. as triangles or as squares. They can be used for implantation of guided or plastic needles into (recurrent) tumours preferably at the apex of the vagina. The needle placement may be guided by endorectal ultrasound. It may also be used for paravaginal implantation and is then fixed to a perineal template.

7.4.2 Perineal templates

Two main perineal templates types have been described in the literature: the Martinez Universal Perineal Interstitial Template (MUPIT) (9) and the Syed-Neblett template (10).

The Martinez Universal Perineal Interstitial Template (MUPIT) (9) (Fig 17.6) was designed to treat not only gynecological malignancies but also prostatic, anorectal and perineal tumors. This applicator consists of two acrylic cylinders, one acrylic template and a cover plate. The template has arrays of holes used as guides for the needles. Guide holes are designed to allow the inserted trocars lie in parallel horizontal planes, perpendicular to the template plane, insuring an adequate geometry of the application. The planes are spaced vertically one cm apart. The distal guide holes are angled 13° laterally, outward to allow a wider coverage of the external part of the tumor, especially parametrial involvement. The 17-gauge needles are stainless steel with a blinded end.
A pre-implant planning takes into account the extents of the tumour in the different planes. Lateral, anterior and posterior limits of the tumour are determined with the corresponding selection of the location of the guide holes in the template. The superior and inferior tumoural limits determine the depth to which the guide needles must be inserted and the number of sources per ribbon. The cylinder length in the vagina is identified according to physical examination.

The implantation procedure is performed under spinal or general anesthesia, with the patient in the lithotomy position. For cervix and vaginal implantation, several sutures are stitched through normal and/or tumoral tissue. A traction of these sutures allows the tumor immobilization during trocar insertion. A Foley catheter is inserted in the bladder. As an intracavitary brachytherapy can be associated with the interstitial brachytherapy, the cervix can be dilated if necessary and a catheter inserted. The sutures are pulled through the central hole of the vaginal cylinder and the cylinder is placed in the vagina with a fixation to the uterine catheter. The template is then fixed to the cylinder with sutures to the perineum. The needles are inserted to the appropriate depth, starting with the needles near the rectum, with one finger inside the rectum to avoid rectal perforation while an assistant pulls gently on the sutures. A second cylinder is placed in the rectum and sutured to the template to assure a fixed distance between the vagina and the rectum and to push away the posterior rectal wall. The rest of the needles are inserted around the vagina and the sutures initially stitched through the tumour and the normal tissues are removed. The template is sutured to the perineum and the cover plate is placed over the template to prevent the needles from displacement. Sterile gauze is placed between the template and the skin. The bladder is maintained distended to keep the small bowel away from the radioactive sources. A rectal tube is inserted with a connection to an intermittent suction.

The Syed-Neblett template (10) (Fig 17.7), originally described as the “transperineal parametrial butterfly”, is based upon the same principle. It consists of two superimposed plastic plates, each 1.2 cm thick, held together by screws. Pre-drilled holes are designed in a concentric “butterfly” pattern to accept the guide needles. Some needles are designed on the surface of the applicator and used in case of anatomical distortions not allowing a proper placement of conventional intracavitary applicators. The needles are fixed to the template by tightening the screws between the two plastic plates. A central hole in the template allows a plastic vaginal cylinder with a central opening which accepts the conventional uterine catheter.
Fig 17.7A,B: Syed applicator with a radiography of an implant.

The implantation procedure is performed under spinal or general anesthesia. The uterine catheter is inserted after cervical dilation. Then, after two markers have been inserted into the anterior and posterior lip of the cervix, the initial needle is inserted into one of the cervical lips to a depth of two to three cm beyond the cervical os. This first needle is very important, as it will regulate the depth of all the other needles secondarily inserted through the template. The vaginal cylinder is then inserted over the uterine catheter which is fixed to each other by tightening screws. The template is then fixed to the vaginal cylinder. The needles are then inserted to a depth indicated by the initial guide needle. Generally, 20 to 30 needles are inserted transperineally through the holes of the template. The initial needle is removed and the needles are maintained in the same position by tightening the screws. Perineal sutures allow the fixation of the template. At the end of the procedure, gauze is placed between the skin and the template.

These templates have allowed the development of interstitial implants. Some problems however arose from the clinical experience. The needle positioning represents one of the limits in the use of such techniques. Despite the design of the templates, the parallelism of the needles is not systematically respected. The needle tips converge or diverge within the pelvic tissues. Several technical modifications have been investigated:

Nag et al (13) developed the use of fluoroscopy to guide the needle placement. These authors used Syed-Neblett applicators (10). Fluoroscopy is used first to check the position of the first guide needle according to the situation of gold markers placed in the cervix or in the vagina. Fluoroscopy was then used after each insertion of a new needle to verify the proper depth, the tip of each needle being generally extended one to two cm above the cervical markers. If needles were not adequately aligned, a reposition was systematically performed, using manual pressure. In this experience based on 71 patients, some needles were repositioned in all cases to improve the parallelism. The modification of the situation of the needles was particularly required in the lateral needles, the medial needles being repositioned more occasionally. The authors recognised however that fluoroscopy was only helpful in the antero-posterior plane. Due to the poor quality of the images provided by fluoroscopy in the lateral plane, the needles could not be modified in this plane and could still be misaligned.

More recently, Stock et al. (21) have developed a technique based on transrectal ultrasound to guide the placement of needles with the Syed-Neblett template (10). The implant procedure starts with the placement of a Foley catheter which is clamped in order to fill the bladder. The extent of the tumour is first assessed with the ultrasound probe used in the cranio-caudal direction. Then, the transverse mode is used from the most cranial to the most caudal image. The lateral and the length
of the tumour are then identified. The longitudinal mode is finally used to identify the total tumoural volume. After this step, the Syed-Neblett template (10) is inserted but the guide needle is not inserted. The dilation of the uterus is performed if necessary. After the template and the obturator (with the tandem if the extent of the tumour required it) have been secured, the needles are placed. The needles are slightly modified with score to enhance echogenicity. The most anterior needles are placed first and they are checked on the transverse plane. The needles are then viewed with the longitudinal imaging, allowing the depth insertion calculation. A special care is taken to insert the needles no further than the tumoral extent, to avoid small bowel damage. The needles are inserted until a total coverage of the target volume. The ultrasound is also used to check the right position of the uterine probe within the uterine cavity. The authors conclude on the interest of the transrectal ultrasound in the accuracy of implants based on 12 procedures (see also Fig 17.8)

Fig 17.8: Ultrasound guided combined intracavitary and interstitial brachytherapy for a large cervix cancer (same patient as in Fig 14.2) with ultrasound guidance of the needles (A) to both posterior-lateral tumour extensions into the sacrouterine ligaments as residual disease outside the cervix at the time of brachytherapy after external beam therapy. MRI assisted treatment planning (B) with delineation of the PTV at the time of brachytherapy including the whole cervix, adjacent parts of the uterine body, and the dorsolateral parametrial extension. The isodoses indicating 75 Gy and 85 Gy (biologically weighted doses) are indicated (PTV 128 cm³), corresponding to the 500 (75 Gy) and 700 cGy (85 Gy) -isodose lines in the figure. DVH analysis (C) showed that 85% of the PTV was encompassed by the 85 Gy-isodose. The 2 cc volume of the rectum received a dose of 79 Gy, 2 cc volume of the bladder 70 Gy.
CT-guided implantation was also described to improve the needle placement accuracy. Erickson et al (14) reported their experience on 25 patients undergoing 28 applications with advanced gynecological malignancies. Syed-Neblett template (10) was used and the needles were placed according to pre-treatment tumor assessment using MRI and intraoperative ultrasound. After the procedure, patients underwent a CT scan. If necessary, a modification in the needle position was possible, because of epidural analgesia. The contribution of CT scan was also determinant to recognize inadvertent rectosigmoid penetration in six patients and in the bladder in four patients so that the needles could be removed or unloaded. A uterine perforation was found in five patients and needles were retracted in three patients because of small bowel penetration. The contribution of CT scan was then considered as an important tool in this type of implant.

![MRI based 3D treatment planning in interstitial gynaecological brachytherapy](image)

**Fig. 17.9 MRI based 3D treatment planning in interstitial gynaecological brachytherapy (Vienna technique):**
Combined intracavitary and interstitial gynaecological brachytherapy with the cervix ring applicator and 4 plastic needles in place on each side (A-C), implanted from the vagina with a small template adapted to the ring (A). Large III B cervix cancer with insufficient remission after 56 Gy to the true pelvis, measuring at the time of brachytherapy 7 cm in width, 6 cm in thickness and 5 cm in height. PTV at the time of brachytherapy and at diagnosis are indicated. The treated volume (700 cGy-isodoseline corresponding to a biologically weighted dose of 86 Gy 180 cc) encompasses the large PTV without leading to a significant overdosage at the rectum or bladder. The 75 Gy isodose is also shown (500 cGy-isodoseline). The 2cc and 5cc values for the rectum as calculated from DVH evaluation are 60% and 50% of the prescribed dose for brachytherapy (total ~70-75 Gy) and for the bladder these are 90% and 80% (total ~80-83 Gy). The left ureter (hydronephrosis) receives a high radiation dose. For details see DVH (D).
Further investigations have evaluated the role of open magnetic resonance imaging using specific titanium-zirconium needles (16). The technical feasibility was achieved with no problems related to the needles, the machine nor the transfer tubes in six patients treated for pelvic tumors. This technique was considered as promising by the authors but required specific MR-compatible instruments. For gynaecological applications the major limitation for MRI guided applications is lithotomy position for placing the needles.

Apart from these technology based non-invasive approaches, invasive surgical procedures combined with interstitial brachytherapy have been described to improve the needle placement. Disaia et al (22) reported an open laparotomy technique. In this situation, the needle placement is guided under a direct visualization from an abdominal approach. The needles can be modified to get not only a good parallelism but also a proper depth with their emergence into the intraperitoneal cavity through the peritoneal surface. In gross disease, the tumour is seen from above and the needles are inserted until they will appear on the top of the tumoural extent. The advantage of such a technique is also the creation of an omental carpet in order to reduce the risk of complications induced by irradiation. Morbidity related to surgery was still observed in 29% of the patients in this population.

In order to decrease this morbidity, laparoscopic procedures were reported. Childers et al (23) reported three patients with a needle placement under laparoscopic guidance with an omental carpet creation. Recio et al (17) used the same approach in six patients with advanced cervical cancers without omental carpet. No complication was observed in relation to this technique. The limitation of these surgical procedures was represented by the inability to visualise extraperitoneal structures, particularly the vaginal area.

All these procedures indicate the need for further investigations in order to determine the best approach in terms of needle placement with respect to the geometry of the application and to the extent of the tumour.

8 Dose, Dose Rate, Fractionation

Due to the complexity of the dose distribution, and the relationship between the loading systems and the dose-rate, it was impossible to separate dosimetry from dose and dose-rate. Different dosimetric systems have been described, according to the type of templates.

In the system described by Charra et al (11), the dosimetry followed the rules of the Paris system. The tumours were all implanted with six needles, with a distance of 12 mm between lines in the majority of the cases. These needles were loaded with 192Iridium wires, the length of which ranged from four to six cm. The total dose depended on the association or not with external irradiation: when interstitial brachytherapy was used as the sole treatment, the mean dose was 54.1 Gy (range: 35 - 72 Gy), and when it was combined with external irradiation, the mean total dose was 27.5 Gy.

In the MUPIT template system (9), the loading depended on the extent of the tumour. In the initial report, the activity was divided into full-strength ribbons and half-strength ribbons. With what the authors called a "judicious" choice between full-strength and half-strength ribbons, the dose rate covering the treatment volume ranged from 0.75 to 1.1 Gy/hour, while the dose-rate decreased to 0.40 Gy/hour 5 to 10 mm outside the target volume. The total activity was in the range of a hundred Ra eq. In the report of a more recent series reported by Gupta et al. (24), the activity per seed was in the central plane approximately one-half to one-third the source activity at the periphery. The implant dose was defined at the transverse plane corresponding to the center of the implant. The total dose ranged from 35 to 37 Gy. The implant was preceded by external irradiation, 36 Gy at 1.8 Gy per fraction. In case of tumoral extension to the pelvic sidewall, a complementary external irradiation
delivered two weeks after the implant, 14 Gy midplane to this area with a central block shielding the volume treated with interstitial brachytherapy.

With the Syed-Neblett applicator (10), the principles of loading were equivalent to the MUPIT. The seed strength generally ranged from 0.30 to 0.45 Ra eq with a total activity ranging from 40 to 70 mg Ra eq. The dose-rate ranged from 0.40 to 0.80 Gy/hour in the volume of interest, while the dose-rate ranged from 0.30 to 0.50 Gy/hour in the rectum and bladder. All the patients reported in the first series (23) had received external irradiation to total dose of 50 Gy to the pelvis with a midline block at 40 Gy. With the interstitial implant, the contribution to point B was about 30 Gy.

The contribution of CT imaging has recently been considered as an aid in the planning of the implant and the dosimetric analysis. Erickson et al (14) described a technique based on CT images allowing the definition of criteria to select an appropriate reference isodose. These criteria included: to avoid a dose rate gradient across the implant greater than 20%, in the central plane the isodose surface (whose value is <125% of the reference isodose) should not be contiguous and its dimensions should be less than two by two cm, the diameter of the hyperdose sleeve (two times the reference isodose) should be less than one cm. With a sophisticated combination of selective unloading or by changing the number of seeds in each needle, the authors arrived at an homogeneous maximum reference dose rate ranging from 0.60 to 0.80 Gy/hour, with rectal and bladder dose rate less or equal to 80% of the reference dose rate. With this approach, dose rate gradients higher than 20% across the central plane of the implant were avoided in the majority of the implants. Total dose to the reference isodose ranged from 25 to 40 Gy, after an external irradiation total dose of 45 Gy. The complexity of such implants also evidenced the limits of prescription points such as point A or point B and the need for further investigation including dose-volume histograms (see Fig 17.9).

Historically, interstitial brachytherapy was used with low dose rate 192 Iridium seeds or wires. Some authors have recently published experiences using high dose rate 192 Iridium remote after loader. In Demanes et al (26) experience, two fractions of either 5.5 or 6 Gy per implant were administered, with at least six hours between the two fractions, usually twelve hours. The implant followed an external irradiation delivering 25 to 36 Gy to the whole pelvis. Subsequent irradiation was given to the pelvic sidewalls with a medline shielding block. The same schedule was actually recommended by the American Brachytherapy Society in Stage IIB/IIIA/IIIB cervical cancers (27). In principle, interstitial brachytherapy applications can also be performed using high dose rate brachytherapy, but only limited experience has been collected so far. This applies for paravaginal and parametrial tumours as well as for tumour recurrences. Treatment planning and the decision on dose and fractionation should follow the same principles as have been developed for HDR brachytherapy in cervix and endometrium cancer in general.

9 Monitoring

The interstitial situation of the radioactive material requires specific attention in terms of pain care. Systematic analgesia is necessary and the intensity of pain may require the use of morphine. Antibiotics are not systematically prescribed but only in case of urinary infection or if fever occurs during the treatment time. The position of the different templates or applicators must be regularly checked in order to avoid radioactive material displacement.
10 Results

10.1 Local control and survival

Available data from interstitial brachytherapy in gynecological malignancies are rather scarce and heterogeneous. Due to the limited number of patients, tumors from different origin and primary as well as recurrences are reported in the same series. The main results are described in Table 1.

In the series reported by Charra et al. (11), the time interval between the initial treatment and the recurrence onset was less than two years in 50 cases. Forty-six patients were treated with brachytherapy alone with a mean dose of 54 Gy while 33 patients were treated with a combination of external irradiation and interstitial brachytherapy with a mean dose of 27.5 Gy.

A univariate analysis of 5-year overall survival rate evidenced recurrence diameter (< 4 cm versus ≥ 4 cm), and age as prognostic factors. In the multivariate analysis of 5-year overall survival rate, only recurrence diameter was identified as a significant prognostic factor with a relative risk of 2.19 for recurrences equal to or larger than 4 cm, with a 95% confidence interval: 1.04-4.6 and p=0.047.

In the initial series reported by Martinez et al. (9) on 35 patients using the MUPIT system radioactive material consists of either permanent implantation of 125-iodine sources or temporary 192-iridium implants. Histology was widely represented: fifteen patients had squamous cell carcinoma, nine had adenocarcinomas, four patients had cloacogenic carcinomas, three had transitional cell carcinomas, two patients had metastatic tumors, one from hypernephroma, one from Hodgkin disease and one patient had small cell carcinoma of the cervix.

Martinez et al. (28) secondarily published a clinical experience accumulated in two institutions: Stanford University and Mayo Clinic with a total of 104 patients. Among them, 37 patients had bulky Stage IIB and III cervical malignancies. The majority of the local failures occurred during the first 10 months of follow-up. Ten patients developed distant metastasis without local failure.

In the experience reported by Gupta et al. (24), disease volume was the sole significant prognostic factor of local recurrence in the multivariate analysis (p=0.011) with a 3-year local control rate of 89% if the disease volume was less than or equal to 100 cc versus 0% when the disease volume exceeded 100 cc. The majority of the patients (12 out of 18) with tumoral volume greater than 100 cc had cervical cancer.

One of the largest experience reported in the literature using the Syed-Neblett template in cervical carcinoma was published by Aristizabal et al. (29,30) with 106 patients. All the patients had primary cervical tumors and were treated with a combination of external irradiation and interstitial brachytherapy. The seven first patients underwent concurrent laparotomies for a better needle placement relative to the target volume and the critical organs. With a mean follow-up of 23 months (12 - 60), local control was achieved in 75% of the cases: 85% in stage IIB, 75% in stage IIIB and 40% in stage IVA. Sixty per cent of the recurrences occurred within six months and 97% within 12 months after the beginning of irradiation.

Hughes-Davies et al. (31) also reported a large number of patients treated in two institutions, Harvard Medical School and Stanford University Medical Center with a total of 139 patients. The conclusion of the authors was a modest chance of patient cure with the template parametrial implant. As stated by these authors however, most of the patients had been selected because of their poor prognosis, with advanced disease.

At the Institut-Gustave-Roussy (31), 150 patients were treated with the use of interstitial brachytherapy. The majority of the patients (137/150) had vaginal or cervical cancers. All patients with primary tumors had advanced cancers: 93% of the patients with cervix cancers had Stage III disease, with 31% of extension to the whole vagina and both complete extension to the parametriae. All the patients received a total dose of 60 Gy, either with brachytherapy alone or combined with
external irradiation, according to the ICRU recommendations. Despite this aggressive therapeutic approach, the major carcinogenic event was represented by local recurrence: 40% of the events.

The vast majority of published data were reported with low dose-rate. Demanes et al. (26) however analysed the outcome of 62 previously untreated patients with either advanced cervical cancer or early stage with unsatisfactory tandem and ovoid placement treated with a combination of external irradiation and interstitial high dose-rate brachytherapy. The scheme of brachytherapy consisted of six fractions of 5.5 to 6 Gy after a dose of 36 Gy of external irradiation followed by a central shielding with a total dose of 50 Gy to the pelvic sidewalls. With a mean follow-up of 40 months, the overall local control was 94%. Local control by FIGO stages was: 100% in stage I, 93% in stage II, 95% in stage III and 75% in stage IV.

In a recent series at Vienna University (93 - 97) 23 patients with centrally recurrent cervix cancer or vaginal recurrence from endometrium cancer were treated with ultrasound guided fractionated HDR brachytherapy (3 - 6 x 7 Gy) with or without EBT (mean 45 Gy). 10 were located at the vaginal apex, 10 at the vaginal wall, 3 in the periurethral region. After a mean follow-up of 30 months, 11 are alive without disease, actuarial local control is 61% and disease specific survival 40%. The main adverse prognostic factors were time to relapse < 2 years, tumour volume at diagnosis >30cc and at the time of brachytherapy >15 cc, tumour extension to the pelvic side wall, total dose <60 Gy. For patients without these risk factors local control was 100%.

Invasive techniques using surgical assistance in needle placement have been reported more as pilot studies than as large series.

In order to better define the role of interstitial brachytherapy in advanced cervical cancer, Bietler et al. (33) examined the sites of recurrence of 26 patients after total pelvic exenteration to determine if local control might have been improved with the addition of intraoperative interstitial brachytherapy. Their conclusion was that brachytherapy had the potential to cure 43% of the patients with local regional failure alone. The potential candidates for this therapeutic approach were patients with close margins, lymphovascular involvement, or perineural invasion.

There has been no randomized trial assessing the role of interstitial brachytherapy versus endocavitary brachytherapy in cervical cancers. A comparison between the two approaches was performed by Monk et al. (34). The authors reviewed the experience of two institutions which individually practiced one of the two techniques. A total of 61 patients with bulky stage II, III, or IVA treated in one institution with endocavitary brachytherapy was compared to a similar series of 70 patients treated with two interstitial implants using the Syed-Neblett template. The two series were comparable in terms of age, tumoral extension, nodal status, and histology. Results showed a two-year disease-free rate in the pelvis of 38% in patients treated with interstitial brachytherapy compared to 45% in patients treated with intracavitary brachytherapy in patients with a brachytherapy dose less than or equal to 4000 Ra mg h eq. When brachytherapy dose was greater than 4000 Ra mg h eq, the rates increased to 47% in the interstitial group and 74% in the intracavitary group (p<0.05). In the subgroup of patients with stage II disease, 5-year local control and disease-free survival rates were significantly greater in the group of patients treated with endocavitary brachytherapy: 61% versus 32% (p=0.01) and 50% versus 21% (p=0.01). One of the explanations for these differences was a larger dose of brachytherapy received by the patients treated with endocavitary techniques because a tandem was used only in 24% of the cases when interstitial techniques were used. No statistical difference was noted in patients with stage III and IVA disease. As stated by the authors however, some bias might have been introduced in the population, specially in terms of patient selection. Patients candidates for interstitial brachytherapy have usually greater tumors than patients treated with endocavitary brachytherapy and the absence of randomization emphasizes the need for further investigations with an adequate methodology.

Interstitial brachytherapy has also been reported in primary vaginal tumors (see vaginal chapter).
Table 17.1: Main results with low-dose-rate brachytherapy

<table>
<thead>
<tr>
<th>Author</th>
<th>Implant system</th>
<th>Patient number</th>
<th>Localisation (P)</th>
<th>Recurrence (R)</th>
<th>Local control</th>
<th>Survival</th>
<th>Complications</th>
</tr>
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<tbody>
<tr>
<td>Charra (11)</td>
<td>Intravaginal template</td>
<td>78</td>
<td>Cervix: 41 Endometrium: 37</td>
<td>R</td>
<td>At 5 years: 70.4%</td>
<td>At 5 years: OS: 56% SS: 62% DFS: 51%</td>
<td>16% Grade 3: 10.2%</td>
</tr>
<tr>
<td>Martinez (9)</td>
<td>MUPIT</td>
<td>35</td>
<td>Cervix: 5 Urethra: 6 Anus: 7 Vagina: 8 Vulva: 9</td>
<td>P+R 88%</td>
<td>At 3 years: 60% P: 50% R: 68%</td>
<td>At 3 years: OS: 41% DFS: 55%</td>
<td>Grade 1-2: Grade 3:</td>
</tr>
<tr>
<td>Martinez (28)</td>
<td>MUPIT</td>
<td>104</td>
<td>Cervix Vagina Urethra Prostate Anorectal</td>
<td>P+R 83.8%</td>
<td>At 5 years: 75%</td>
<td>At 5 years: OS: 35% DFS: 30%</td>
<td>Grade 4/104 3:</td>
</tr>
<tr>
<td>Gupta (24)</td>
<td>MUPIT 24 pts with interstitial hyperthermia</td>
<td>69</td>
<td>Cervix Endometrium Vagina Urethra</td>
<td>P+R</td>
<td>At 3 years: 57 months</td>
<td>At 5 years: DFS: 32% CSS: 33%</td>
<td>Grade 14:</td>
</tr>
<tr>
<td>Aristizabal (29, 30)</td>
<td>Syed-Nebielt template</td>
<td>106</td>
<td>Cervix</td>
<td>P</td>
<td>Mean FU: 23 months 75%</td>
<td>At 5 years: DFS: 32% CSS: 33%</td>
<td>Requiring surgery: 17%</td>
</tr>
<tr>
<td>Hughes-Davies (32)</td>
<td>MUPIT</td>
<td>139</td>
<td>Cervix Vagina/Vulva: 20 Endometrium: 14 Rectum: 6 Palliative: 5</td>
<td>P+R Median FU: 57 months</td>
<td>Median FU: 57 months At 5 years: 25%</td>
<td>At 5 years: DFS: 32% CSS: 33%</td>
<td>Grade 3-4:</td>
</tr>
<tr>
<td>Haie-Meder (31)</td>
<td>GG, PT, Syed-Nebielt template</td>
<td>150</td>
<td>Cervix Vagina Urethra Vulva</td>
<td>P:101 R:49</td>
<td>At 5 years: 60%</td>
<td>At 5 years: OS: 35% DFS: 30%</td>
<td>Grade 11/135</td>
</tr>
</tbody>
</table>

FU: follow-up  
OS: overall survival  
SS: specific survival  
DFS: disease free survival  
CSS: cause specific survival  
GG: guide gutter  
PT: plastic tube  

10.2 Complications

Complications were differently reported depending upon the type of tumours, the tumoural size, the treated volume, the follow-up of the population and the type of complication scoring system. The reported incidence of complications was generally higher than with endocavitary brachytherapy. The general incidence of complications described in the literature are reported in Table 17.1.

Charra et al. (11) reported a significantly higher complication-rate in the group of patients who had received irradiation as a part of the initial treatment (p=0.001).
In the initial experience reported by Martinez et al. (9), two out of 35 patients developed major complications: one necrotic rectal ulcer which required colostomy and one contracted painful bladder which necessitated urinary diversion. In the report on a total of 104 patients treated with interstitial brachytherapy, 37 of them presenting with advanced cervical cancers, Martinez et al. (28) reported four major complications. Among them, two occurred in the 37 patients treated for advanced cervical carcinomas. A tendency for complications to increase was observed when the dose of external irradiation exceeded 50 Gy.

In the series reported by Gupta et al. (25) hyperthermia or prior irradiation did not appear to increase the complication rate. A dose-rate of less than 70 cGy/hour appeared to significantly increase the risk of grade 4 complications in the limit of a univariate analysis.

Aristizabal et al. (29) reported their complications using a specific classification in three grades. Eighteen per cent of the patients presented with grade II and III, with 6 of the 19 patients developing vesico- or recto-vaginal fistulae while 6 other patients developed rectal stenosis, three requiring colostomies. The frequency of the complications was correlated with the geometric distribution of the radioactive sources. The loading of the obturator needles leading to high doses to the vaginal mucosa was associated with a higher incidence of complications: 64% of the patients with this source arrangement developed severe complications while only 19% of the patients presented severe side effects when the obturator needles were not loaded.

In the series reported by Hughes-Davies et al. (32), late complications requiring surgical intervention were observed in 17% of locally controlled patients, with a 4% rate of fistula, 11% bladder complications and 17% bowel complications.

Demanes et al. (26) reported their experience with high-dose rate interstitial brachytherapy in 62 patients. Grade 3 - 4 complications were observed in 6.5% of the patients. These complications consisted of one vesicovaginal fistula, one vaginal necrosis leading to a fatal hemorrhage, and two small bowel obstructions.

In the recent Vienna series with HDR interstitial brachytherapy in 23 patients complications mainly occurred at the vagina: 9 patients with atrophy, 6 patients with significant shortening and narrowing, 2 patients with obliteration. One patient developed a ureteral stricture requiring surgery, one a malabsorption syndrome. No severe complications were seen at the rectum or bladder.

In the series reported by Monk et al. (34) in an attempt to compare interstitial and intracavitary brachytherapy, the same serious complication rates were observed in the two groups, and reached 21% in each group. The most frequent complications were from digestive origin: intestinal obstruction was encountered in 4% in the interstitial group and 10% in the intracavitary group respectively. Digestive fistula occurred in 9% in the interstitial group and 3% in the intracavitary group respectively. Seven per cent of the patients in the interstitial group and 2% in the intracavitary group respectively experienced severe proctitis. Urinary complications were observed in 3% of the patients in the interstitial group and 2% in the intracavitary group respectively.

13 References


