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Primary Vaginal Cancer

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1 Introduction

Primary vaginal cancer is rare, accounting for 2% of gynaecological malignancies. To confirm the diagnosis of primary vaginal cancer, two conditions are necessary: the cervix must be healthy, and if hysterectomy has been performed within 5 years for a uterine tumour, the histopathology must differ from that of the uterine tumour.

Adult vaginal malignant tumours occur mainly in postmenopausal women (80%) and the mean age ranges from 60 to 65 years. (15)

Etiological factors include HPV infection, particularly in the case of multiple gynaecological malignancies. (9) Other risk factors such as previous hysterectomy or prolapsed uterus treated with a pessary have been proposed. (15)

Symptoms are comparable to those from cervical cancers including discharge, bleeding or pain during sexual intercourse. In more advanced stages, patients can present with inguinal adenopathy and/or urinary and rectal signs. (9) As older women may be less sexually active, diagnosis can be delayed.

Prognostic factors include clinical stage, age, non-epithelial tumours; the influence of tumour site is more controversial. (19)

Surgery can be proposed in superficial and limited disease of the upper third of the vagina or close to the vulva, particularly in young patients. In more extensive tumours, surgery often requires multivisceral sacrifice. (15) For this reason, the majority of patients are treated with definitive irradiation combining external beam irradiation and brachytherapy. (12,21,22) For patients presenting with small volume well circumscribed disease, brachytherapy alone may be indicated. (8)

2 Anatomical Topography

The vagina is a pseudo-cylindric expandable cavity, between bladder and rectum, which represent the two main critical organs. The vagina is limited by the cervix superiorly and by the urethral meatus and the labia minora inferiorly.

The vagina extends laterally to the paravaginal and parametrial tissues, anteriorly to the bladder and urethra and posteriorly to the rectum.

The lymphatic drainage of vaginal tumours is correlated to the double embryologic origin of the vagina (Müller canal and urogenital sinus): the upper two-thirds to iliac nodes, lower third to hypogastric and inguinal nodes. The drainage of the posterior septum is to the hemorroidal and sacral nodes. (9)

3 Pathology

Three macroscopic types have been reported (8,9,15): superficial (5 - 10%), exophytic and ulcerating (50 - 70%), infiltrating (25 - 35%). The preferential primary sites are upper third posteriorly and lower third anteriorly, but 40 to 50% of tumours are multifocal.

The histological types are: squamous cell carcinoma (80 - 85%), adenocarcinoma (10 - 15%), sarcoma and melanoma (2 - 3%) and others (1 - 2%). (8,9)

4 Work Up

Local primary disease assessment requires a very careful gynaecological examination, if possible by more than one physician, and may need general anaesthesia. It is important to exclude a tumour arising elsewhere and involving the vagina (most often cervix cancer) or metastases into the vagina, e.g. from gynaecological tumours (endometrium, ovarian cancer) or other malignancies. (9,15) The site of the tumour within the vagina, the macroscopic characteristics (exophytic and/or ulcerative growth), and any regional spread outside the vagina must be carefully assessed and documented. (8)
A vaginal imprint (Fig 16.1) is the most adequate documentation of intravaginal tumour topography and morphology and should be systematically performed (see chapter 14 on cervix). (10)

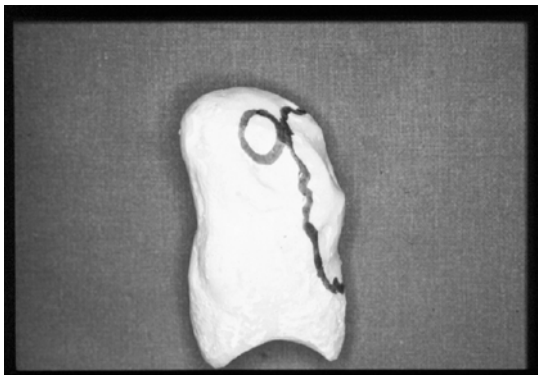


Fig 16.1: Vaginal impression showing a tumour extension to the left antero-lateral vaginal wall, allowing the GTV determination, first step of the vaginal mould construction.

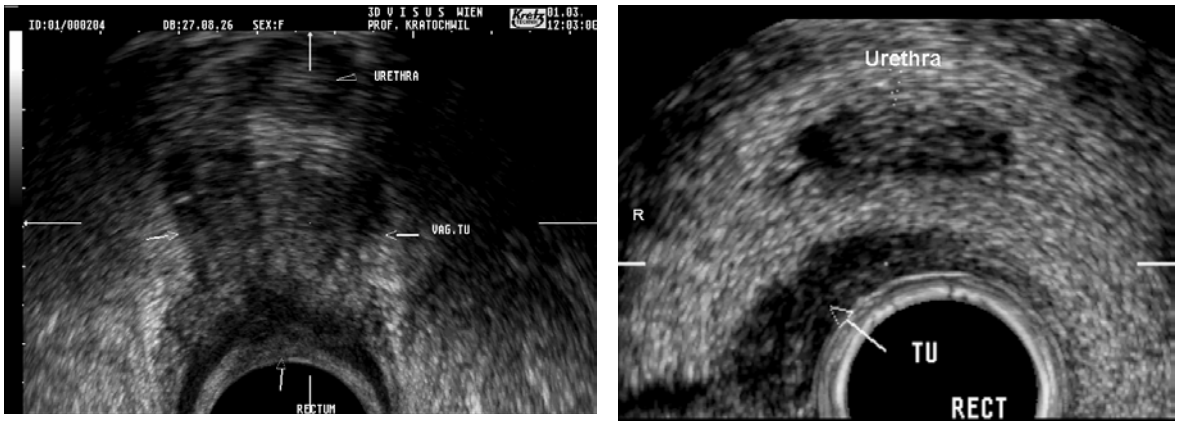


Fig 16.2: Endosonography for vaginal cancer
A: Large vaginal cancer with infiltration of the rectal wall
B: Small vaginal cancer 6.7 mm in its maximum thickness involving a part of the vaginal circumference (20 mm), length 15 mm; urethra is indicated

The final diagnosis is based on the histopathological report of a biopsy. It is often necessary to perform several biopsies at different vaginal levels.

Transvaginal and/or transrectal sonography helps to check precisely the morphology, the location and the topography of the tumour in the vagina (Fig 16.2). MRI (CT) accurately assesses tumour extension into the paravaginal tissue (Fug 16.6).
Sectional imaging methods, in particular CT and MRI, may also be used for assessing topography of bladder, rectum, sigmoid, and intestine (see chapter on cervix).

Further diagnostic examinations may be indicated dependent on the tumour extension: rectoscopy and/or cystoscopy to exclude organ involvement in locally extensive disease; pelvic and abdominal ultrasound, CT scan or MRI to detect regional and/or distant lymph node metastases; intravenous pyelography to exclude ureteral obstruction; chest radiography to exclude lung metastases (see chapter 14 on cervix).

Before a final decision about the treatment, general examination and appropriate investigations are performed taking into account especially the general condition of the patient.

Tumours are staged according the TNM/FIGO-classification (See appendix): T0 for superficial non-invasive lesions; T1/stage I for lesions confined to the vaginal wall; T2/stage II for lesions extending into the paravaginal tissue; T3/stage III for lesions reaching the pelvic wall; T4/stage IVA for lesions involving bladder and/or rectum.

5 Indications, Contra-Indications

In limited disease (T0/T1 N0), brachytherapy alone is indicated. In the upper vagina and close to the vulva, surgery represents an alternative approach in particular in young patients in order to preserve ovarian function. (9)

In more advanced disease (extensive T1/T2), brachytherapy is indicated in combination with external beam therapy. (12,21)

In locally extensive disease (T2/T3), external beam therapy is systematically combined with brachytherapy. (14,21,22)

Concomitant Cis-Platin based chemotherapy can be proposed in locally extensive disease, as indicated in cervix cancer (see chapter 14 on cervix).

6 Target Volume

The clinical target volume assessment depends on both clinical examination and complementary imaging examinations. Local as well as lymphatic extension must be taken into consideration for the determination of the target volume for external beam irradiation and for brachytherapy.

In the case of well defined, more superficial tumours, the target volume is easy to define: it includes the GTV plus a safety margin of 10 to 20 mm along the vaginal wall. For large and/or multicentric tumours, the target volume related to the GTV in the vagina often includes the whole vagina and any extravaginal extension and is more difficult to assess. Infection is often present, increasing the difficulties of evaluating the tumour volume. It is often necessary to include the whole vaginal cavity.

Depending on the tumour extension, the target volume may also include paravaginal and/or parametrial involvement.
For each patient, the overall target volume must be defined before any treatment. If the first treatment is external beam therapy, the target volume at the time of brachytherapy must be the initial infiltrating tumour volume plus a safety margin (Fig 16.3). The GTV at the time of brachytherapy +/- some safety margin may also be taken to define a certain dose level to be applied to this volume. (compare Fig 16.6).

We recommend to focus on two aspects of the target volume: first inside the vaginal cavity itself and secondly, the extension outside the vaginal wall. This discrimination represents the first step in choosing the technical brachytherapy approach: intracavitary, interstitial or a combination of both. (8,9,22)

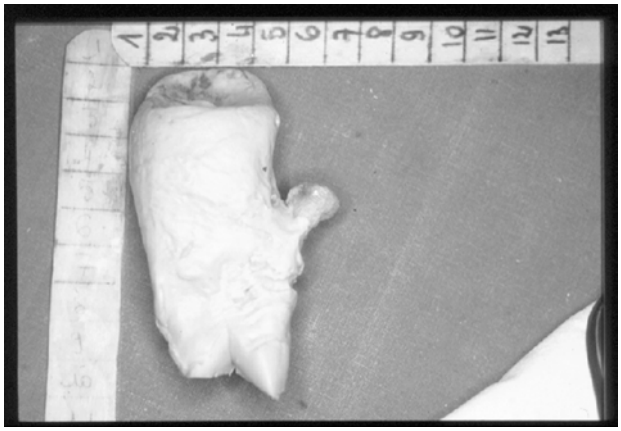


Fig 16.3: Vaginal impression of an ulcerative tumour treated first with external irradiation. The brachytherapy boost is given with the guide gutter technique and shown in the interstitial brachytherapy in gynaecological cancers (Fig 17.3).

7 Technique

7.1 Implants

Intracavitary as well as interstitial implants are used, often in combination. For intracavitary implantation different dose rates can be used, for interstitial brachytherapy the largest experience is based on low dose rate brachytherapy (LDR).

7.1.1 Intracavitary brachytherapy

Different vaginal applicators have been described: metallic or plastic colpostats, cylinders of different diameters and sizes, ring applicators, or a vaginal mould, to be adapted to the anatomy of the patient, to the volume and the topography of the tumour. (5,10,12,18) In tumours of the upper third of the vagina, the technique is analoguous to that in cervix cancer (see techniques 14.7 in cervix cancer).

Applicators specifically dedicated to vaginal treatments, including vaginal cancers have been described (compare in detail the chapter on endometrial cancer). These are vaginal cylinders with a central hollow metallic cylinder. (6) The sources are located within the metallic cylinder. A plastic ring 2.5 cm in length covers the cylinder. The plastic rings have different diameters, depending upon the vaginal size, ranging from 2 cm to 4.5 cm, 5 mm apart. These domed cylinders are used to irradiate the vaginal cuff. Vaginal cylinders can be added to the dome cylinders, depending upon the extent of the tumour. Some cylinders have lead shielding to protect part of the vaginal wall, rectum, bladder or urethra. In order to avoid any applicator rotation, a flange is placed over the tandem just after the last cylinder.(6)

Perez et al. (18) designed a vaginal applicator called MIRALVA (Mallinckrodt Institute of Radiology After Loading Vaginal Applicator) (Fig 16.4), which incorporates two ovoid sources and a central tandem. This device can be used to treat the entire vagina. It has vaginal apex caps and additional cylinder sleeves allowing for increasing dimensions.

The Gustave Roussy-Technique (9,10,15) is based on the use, as for cervix carcinoma, of moulded applicators. The description of this technique is given in detail in the chapter of cervix carcinoma. The first step of the technique consists of a vaginal impression which shows accurately the topography of the tumour, and if the moulded applicator is not used, it still facilitates the choice and adaptation of a standardised applicator (Fig 16.1, Fig 16.3). This individually adapted applicator helps to improve the ballistic selectivity of the vaginal implant even for very irregular target volumes. This technique improves local control with lower complication-rate (Fig 16.3).

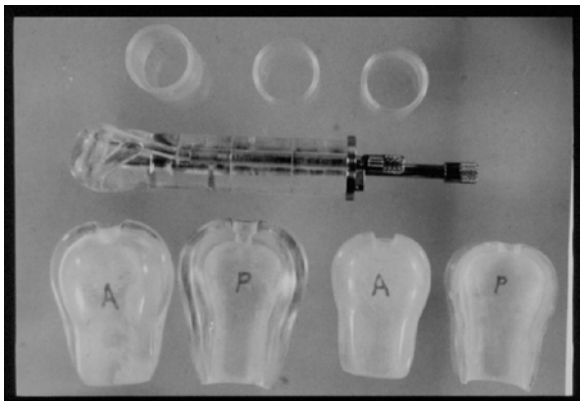
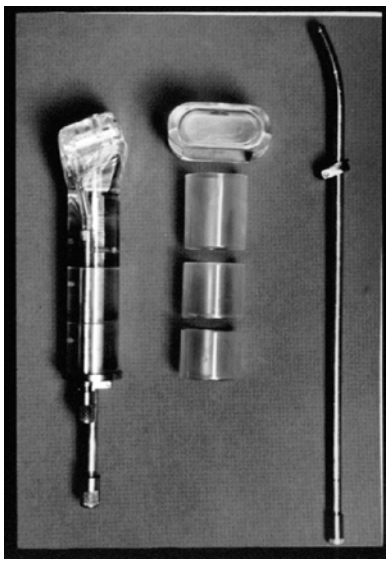
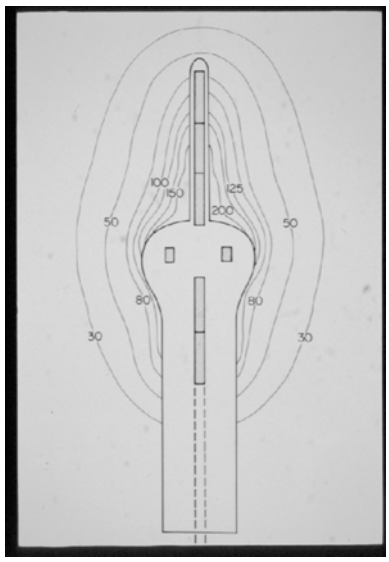
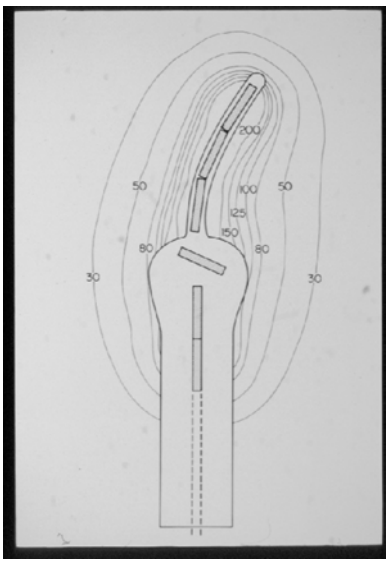


Fig 16.4: MIRALVA applicator
(courtesy of Carlos Perez)







In HDR brachytherapy according to the Vienna experience for intravaginal brachytherapy, standard cylindrical vaginal applicators with one central intravaginal tube are used which vary in diameter (25-35 mm, see above). These applicators are identical to those used for postoperative brachytherapy in endometrial cancer. These applicators are also available with a metallic shielding device for one, two or three quarters of the cylinder over the whole length of the applicator. In tumours limited to the

upper third with an intact cervix, ring applicators are used (compare chapter on cervix). In difficult cases specific cylindrical plastic applicators are used that as well as the central hole have specific holes near to the applicator surface for introducing tubes or needles according to the needs of the specific tumour extension. Such an applicator may be rigidly linked to a template for the paravaginal and/or parametrial needles or tubes.

7.1.2 Interstitial implants

The technique and the principles of interstitial brachytherapy are described in a specific chapter (Chapter on interstitial brachytherapy in gynaecological cancer). Different afterloading techniques can be used depending on the size and the site of the tumour and also on the experience of the different schools of brachytherapy employing different dose rates (Fig. 16.5 -7).

7.2 Radioactive sources

For LDR-brachytherapy two main types of sources are used: iridium for interstitial implants and intracavitary brachytherapy, caesium for intracavitary brachytherapy. In the system reported by Delclos et al. (5,6), a short caesium source is recommended at the top of the dome cylinder to obtain a uniform dose around the dome.
In the moulded applicator system, (10,15) the length of each source is selected according to the target volume. The distance between the different sources must be equal. Two kinds of sources can be used: iridium when the vaginal mould is small, caesium when the dimensions of the mould are larger.

Iridium is the main source used for HDR brachytherapy. (12)

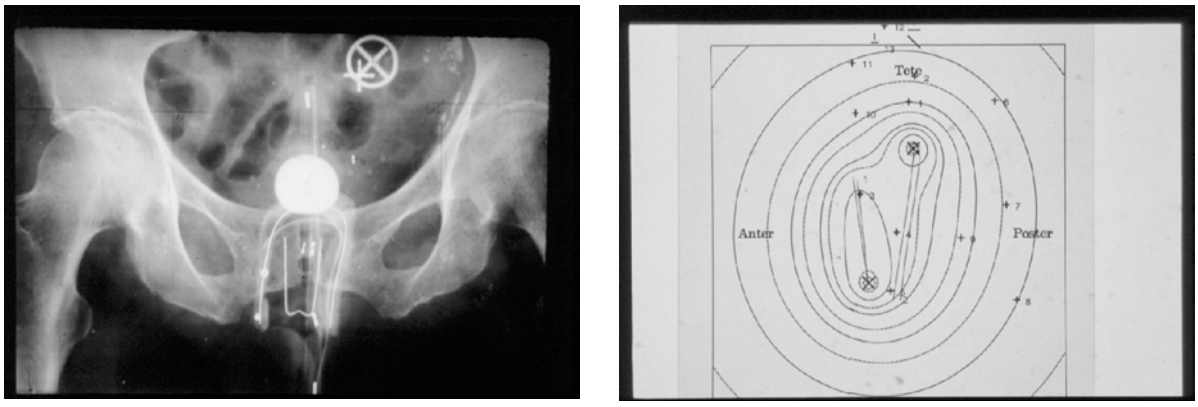
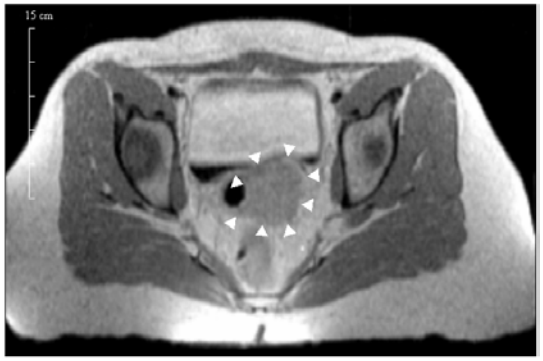


Fig 16.5: Interstitial and intracavitary Iridium implant for a limited anterior wall vaginal tumour, combining hairpin and mould applicator:
A: AP radiograph; B: Dosimetry in the sagittal plane.

8 Dose Calculation and Treatment Planning

In the system reported by Delclos et al. (5,6) the curvature of each dome cylinder follows an isodose of the sources.

In the MIRALVA device, (18) when there is no intrauterine tandem, the regular ovoid size is loaded with two 20 mg Ra eq Cs tubes. According to the tumour extent, the distal vaginal cylinders can be loaded with 10 mg Ra eq sources and the most distal sources can also be loaded with 15 to 20 mg eq sources.



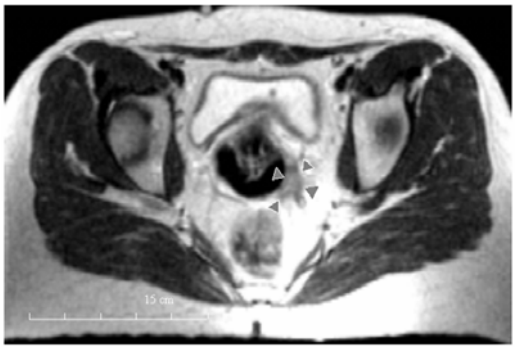


Fig 16.6A/B: MRI at diagnosis (tumour dimension: 4 cm height, 6 cm width, 3 cm thickness), and after radiochemotherapy at the time of the first intracavitary implant indicating residual extravaginal tumour spread (dimension: 2 cm height, 2 cm width, 2 cm thickness);

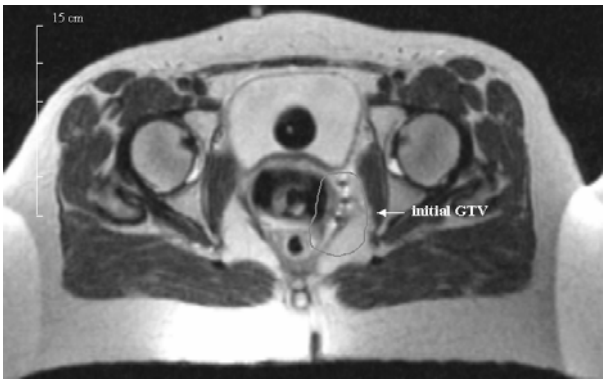
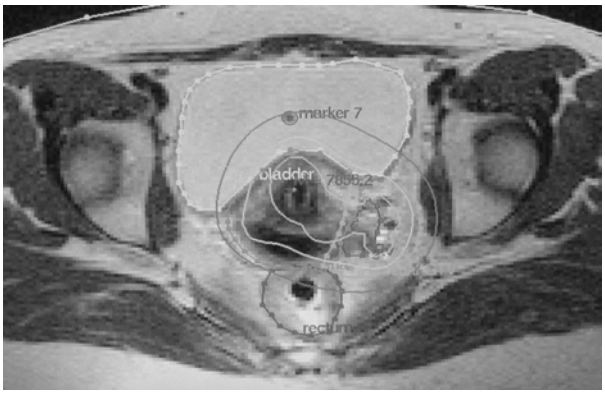


Fig16.6C: MRI with the second combined intracavitary (ring applicator) and interstitial brachytherapy in one plane with three plastic needles inserted parallel to the axis of the vagina.



16.6D: Computer assisted dose calculation in a transversal plane with the treated volume encompassing the GTV + safety margin. Total isoeffective dose (alpha beta value of 10) at 5 mm vaginal tissue depth was 85 Gy and 80 Gy at the GTV plus safety margin.

Fig 16.6 Interstitial and intracavitary HDR Iridium implant for an extended upper vaginal tumour (clinical stage III) after 45 Gy EBRT (including the whole vagina) and cis-Platinum 40 mg/m^2/week. The lateral wall of the upper vagina revealed an exophytic and ulcerative tumour infiltrating into the left paravaginal tissue reaching the pelvic wall. Total dose of BT was 4 x 7 Gy at 5 mm tissue depth in the upper half of the vagina and 3 x 7 Gy in the GTV at the time of BT (plus safety margin).

In the IGR moulded applicator system, when intracavitary brachytherapy alone is performed, the reference isodose is chosen according to the dimensions of the PTV. If interstitial implants, Paris

system rules are applied for the implantation itself, and for dose calculations. For these two kinds of brachytherapy are combined, ICRU 38 recommendations can be applied for reporting.

Fig 16.7: Ultrasound assisted interstitial brachytherapy of an anterior vaginal cancer (stage II) after 40 Gy EBT to the true pelvis.

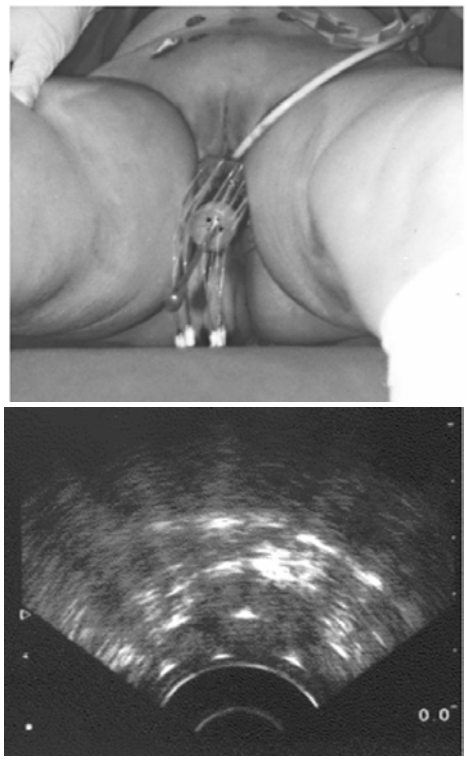
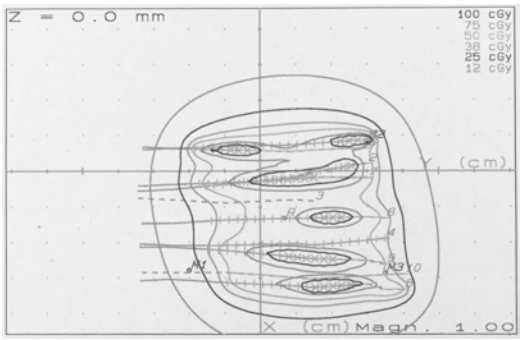


Fig 16.7A:Clinical setting with the intravaginal applicator (with holes for needles near the vaginal wall) combined with a fixed template for the extravaginal needles; 7 needles in place.
Fig 16.7B: Transverse ultrasound during the intervention with 5 needles inserted in triangle geometry. In the anterior part of the tumour the urethra can be seen, which is marked by a catheter.
Fig 16.7C: Localisation X-ray with 9 needles, intravaginal applicator in place, urinary catheter and the bladder filled with contrast medium.

In HDR brachytherapy in vaginal cancer (12,16) the isodoses follow the round curvature of the plastic cylinder surface. The dose is prescribed to the vaginal wall (PTV) for a certain length (part of the vagina, whole vagina) and depth and is reported at 5 mm radial distance into the vaginal wall. If (additional) interstitial brachytherapy is given, the dose is prescribed to the extravaginal GTV at the time of brachytherapy +/- safety margin (Fig. 16,6 and 7). The dose is calculated and reported according to the recommendations of ICRU report 58 (Fig 16.7D-F).

Fig 16.7: Ultrasound assisted interstitial brachytherapy of an anterior vaginal cancer (continued)



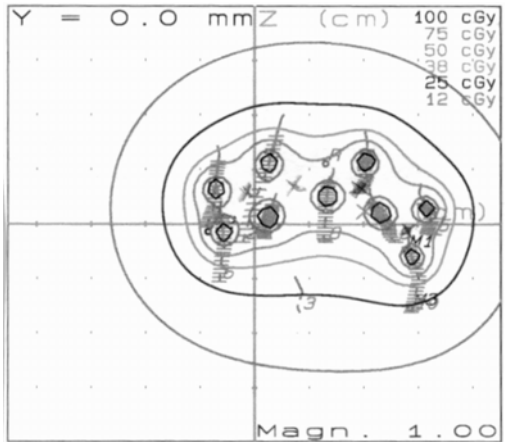


Fig 16.7D,E: Dose distribution in the transverse and coronal plane with marking of the mean central dose (MCD) (62 cGy) and the reference isodose which was chosen to be 80% of the MCD. Reference dose was 50 cGy per hour with a total dose of 35 Gy at the 80% isodose (PDR). 150% of the reference isodose and of the MCD are shown (overdosage volumes).

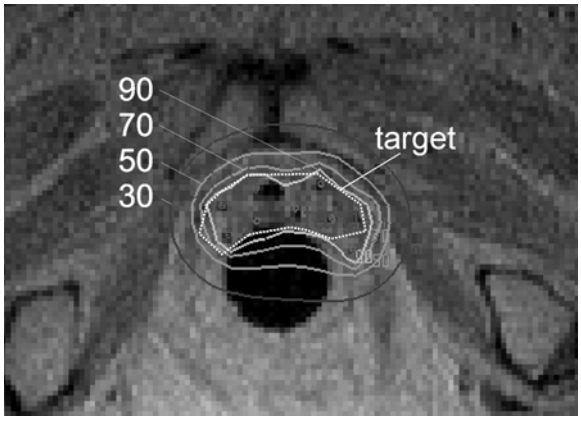


Fig. 16.7F: MRI assisted treatment plan with PTV and isodose distributions in % of the reference isodose (50 cGy): 90, 70, 50, 30.

9 Dose, Dose Rate, Fractionation

In the system reported by Delclos et al., (5,6) the vaginal surface dose ranges between 70 Gy and 80 Gy when brachytherapy is the sole treatment and 40 Gy and 50 Gy when external irradiation is combined with brachytherapy.

In the MIRALVA device, (18) when there is no intrauterine tandem, the source arrangement is designed to obtain a surface dose rate of approximately 1.2 Gy/hr at the vaginal apex surface. These loadings usually result in surface dose-rates at the distal part of the vagina of approximately 80% to 90% of the surface dose on the apex.
With the IGR technique, (9,15) if brachytherapy is done alone, the total delivered dose to the PTV is 60 Gy, given at a daily dose rate of 12 - 18 Gy and the report follows the rules of the ICRU

recommendations (Fig 16.5). In case of combination of external beam irradiation with brachytherapy boost, the dose of the boost is by convention 60 Gy minus the dose of external beam irradiation (see cervix chapter).

In the recent Vienna HDR brachytherapy approach, the dose is 5 - 6 x 5 - 7 Gy at 5 mm tissue depth for brachytherapy alone in superficial tumours, which corresponds to 8 - 12 Gy applicator surface dose. In locally advanced disease, the dose is 45 - 50 Gy EBRT to the PTV including the whole vagina, the extravaginal tumour extension, the areas at risk for local spread and lymph node areas at risk. Dependent on tumour remission, intravaginal ± interstitial brachytherapy is added with 3 - 4 fractions of 5 - 7 Gy. The dose is reported at 5 mm into the vaginal wall and at the extravaginal part of the CTV as defined at the time of brachytherapy if additional interstitial brachytherapy is given. Total isoeffective dose (alpha beta value of 10) at 5 mm vaginal tissue depth and at the CTV as defined at the time of brachytherapy is calculated to be between 75 and 90 Gy (see Fig 16.6 and 7).

10 Monitoring

For intracavitary brachytherapy alone, monitoring for cancer of the vagina is quite comparable to monitoring for cancer of the cervix.

For interstitial implants, the risk of local infection and pain is higher. Systematic prophylactic antibiotic treatment can be prescribed routinely or used only in case of symptoms.

11 Results

One of the first large reports was from Kucera et al. (11) on 434 patients treated in Vienna from 1952-1984. Intracavitary radium was the standard treatment for more than two thirds of the patients. The data were focused on the 110 patients treated during the last years. The five-year survival rate was according to the stages: 76.7% in Stage I, 44.5% in Stage II, 31.0% in Stage III and 18.2% in Stage IV. The data were recently updated, (12) with a historical comparison between high-dose rate and low-dose rate. There was no significant overall difference in local control and survival between the two treatment modalities.

The experience of the M.D. Anderson Hospital was reported by Chyle et al. (3) in 1996, with a total of 301 patients treated between 1953 and 1991. The majority of the patients were treated with a combination of external irradiation and brachytherapy. The median follow-up of the patients was 13 years. The 5-year, 10-year, 15-year, 20-year, and 25-year survival rates were 60%, 49%, 29%, and 23% respectively. Three factors which independently correlated to local recurrence were identified: tumour size (<5 cm versus >5 cm), tumour site (upper versus middle or lower versus whole vagina), and circumferential location (posterior versus all other locations). Severe complications occurred in 39 patients, and the 20-year actuarial serious complication-rate was 19.

Perez et al. (18) evaluated the prognostic and technical factors of 212 patients with primary vaginal cancers treated with definitive radiation therapy. Tumour stage appeared to be the most important prognostic factor. Actuarial 10-year survival was 94% in Stage 0, 80% in Stage I, 55% in Stage II, 35% in Stage III, 0% in Stage IV. Patients with Stage I disease had the same local control if brachytherapy was the sole treatment or if brachytherapy was combined with external irradiation. The incidence of distant metastases was high, 13% in Stage I, 30% in Stage IIA, 52% in Stage IIB, 50% in Stage III, and 47% in Stage IV. The incidence of grade 2 - 3 complication was 7%.

Table 1: Results for treatment of vaginal cancer

Authors	Pts	FIGO Stage	Treatment	Brachy	Survival %	Local control %	Complications %
Chyle (3) (Delclos) (6)	301	0 37 I 65 II 122 III 60 IVA 17	A, B, C		OS 60	ALC 77	19 at 20 yrs
De Crevoisier (4)	103		B 98	LDR ICBT 68 LDR IBT 5 ICBT+IBT 28	OS I 67 II 61 III 35 IV 20		14 (Gr 3)
Dixit (7)	70	I 8 II 10 III 15 IV 7	A, B		2yr OS I 100 II 70 III 14 IV 0		
Kucera (11)	110				I 77 II 45 III 31 IV 18		
Lee (13)	65	0 16 I 17 IIA 6 IIB 10 III 20 IVA 6	A, B++		CSS 0 100 I 94 IIA 80 IIB 39 III 79 IVA 62	0 100 I 87 IIA 88 IIB 68 III 80 IVA 67	12 (Gr3
Leung (14)	103		B 74 D 10	2nd period more IBT	2nd period 61/30	I, II 2nd period 95/60	
Perez (19)	212				10-yr AS I 80 II 55 III 35 IV 0		7 (Gr 2-3)
Schäfer (21)	39	I 17 II 9 III 9 IV 4	B	Ra	AS I 62 II 44 III 25		
Tewari (22)	71	I 10 II 39 III 15 IV 7	A61 B 10	IBT Ir	ADFS 58 I 100 II 60 III 30 IV 0	75	

legends: A: Brachytherapy alone - B: EBRT + brachytherapy - C: EBRT alone - D: Surgery + Radiotherapy - ADFS: Actuarial Disease-Free Survival

Concluding the table, the total number of patients analysed is 383 + 1074 (including the literature review by Nanovati on 12 studies of stage-I -II vaginal cancer (CP)). 80 to 90% of patients were treated by external beam radiation and LDR brachytherapy. Overall survival and local control rates were 5-60% and 70% respectively. Stage-by-stage survival and local control rates were 75% and 80%, 60% and 70%, 40% and 55% for stages I, II and III respectively.

The latest retrospective study at Gustave Roussy Institute included 103 adult patients treated between 1970 and 1998. (4) Most patients (98 out of 103, 95%) were treated with external irradiation, combined with brachytherapy in 85 patients (82%). The mean total dose of external irradiation was 50 Gy (range: 9Gy - 50Gy). The mean dose delivered by brachytherapy was 10 Gy with endocavitary customized mould applicator in 68 patients, interstitial technique in 5 patients and a combination of endocavitary and interstitial in 28 patients. The mean 60 Gy volume, according to ICRU recommendations, was 243cc. With a median follow-up of 89 months, the 2-year, and 5-year overall survival rates were 79% and 67% in Stage I, 76% and 61% in Stage II, 61% and 35% in Stage III, and 20% and 20% in Stage IV respectively. Significant prognostic factors were: the number of involved vaginal segments, FIGO Stage, age, response to external irradiation assessed at the time of brachytherapy, and treatment duration (median: 60 days). Fourteen grade 3 complications (Franco-Italian glossary) were observed, the majority being vaginal complications: 8 out of 14.

In a retrospective study on fractionated HDR brachytherapy with or without EBRT in Vienna, 86 patients (mean age 71 years) consecutively treated from 1986-1998 were investigated. (16) Classification according to FIGO revealed 6 patients in stage 0, 16 in stage I, 39 in stage II, 20 in stage III, and 5 in stage IV. For early disease 26 women received intravaginal brachytherapy alone, for locally advanced disease 55 women received external beam irradiation (mean total dose 49 Gy) combined with intravaginal brachytherapy. In 8 women, individualized interstitial brachytherapy was added in recent years for extravaginal residual disease. At the applicator surface the physical dose per fraction was 9 - 15 Gy and the total dose of brachytherapy varied with the number of fractions (n=2-6). With a median follow - up of 30 months (range 2 - 135), the number of local recurrences were 27 with 0/6 in stage 0, 2/16 in stage I, 13/39 in stage II, 9/20 in stage III and 3/5 in stage IV. The 3 year disease specific survival was 78% and the overall survival was 56%; according to stage 100/80% (0), 83/54% (I), 74/46% (II), 63/53% (III) and 26/20% (IV), respectively. Late side effects, which were retrospectively evaluated in 40 patients alive (10 patients with Grade 3/4 according to the EORTC score), were seen as Grade 3/4 for the bladder in 1/1 patients, for the rectum in 2/2 patients and for the vagina in 1/3 patients, respectively.

Some authors have reported different results as a function of tumour site. Ali et al. (1) showed better survival in patients with cancer in the proximal half of the vagina as compared to the distal half: 81% versus 41%. The total number of the patients in the study however was only 40.

The role of interstitial techniques in the treatment of vaginal cancers remains controversial. Leung et al. (14) for instance have reported a series of 103 patients treated between 1970 and 1989. After 1985, better local control was achieved and the authors claim that the more systematic use of interstitial brachytherapy explains this improvement. Stryker (21) also recommends the use of systematic interstitial techniques in vaginal cancers, based on his experience in 34 patients. Tewari et al. (22) recently described a series of 71 patients treated for primary vaginal cancers with interstitial brachytherapy using the Syed-Neblett applicator. Sixty-one patients (88%) received external irradiation to a total dose of 50.4 Gy with a midline block during the last part of the treatment to limit the bladder and rectal doses to 40 Gy. The interstitial dose was based on the stage of the disease and ranged from 16.5 Gy to 22 Gy. With a median follow-up of 66 months, the actuarial local control was 75%. The 2-year, 5-year, and 10-year actuarial disease-free survival rates were 73%, 58%, and 58% respectively. Severe complications occurred in 13% of the patients.

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