Primary Invasive Carcinoma of the Vagina

Treatment with Interstitial Brachytherapy

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BACKGROUND. Because primary carcinoma of the vagina comprises less than 2% of all gynecologic malignancies, the reported experience in the treatment of large numbers of patients is available only from a few major centers and most often encompasses a variety of differences in treatment selection and technique. The objective of this study was to assess the long term results of an interstitial iridium-192 afterloading implant technique using the Syed-Neblett dedicated vaginal plastic template.

METHODS. Patients who were treated from 1976 to 1997 were examined retrospectively.

RESULTS. Seventy-one patients underwent interstitial implantation with (n = 61 patients) or without external beam radiotherapy. The median age was 59 years (range, 16–86 years). Patients were staged according to the International Federation of Gynecology and Obstetrics system and included Stage I (n = 10 patients), Perez modification Stage IIA (n = 14 patients), Perez modification Stage IIB (n = 25 patients), Stage III (n = 15 patients), and Stage IV (n = 7 patients). Each implant delivered an approximately 20-gray (Gy) minimum tumor dose, with the total tumor dose reaching 80 Gy with integrated external beam radiotherapy. Local control was achieved in 53 patients (75%). The median follow-up was 66 months (range, 15–163 months), and the 2-year, 5-year, and 10-year actuarial disease free survival rates are 73%, 58%, and 58%, respectively. By stage, 5-year disease free survival rates included Stage I, 100% of patients; Stage IIA, 60% of patients; Stage IIB, 61% of patients; Stage III, 30% of patients; and Stage IV, 0% of patients. The factors disease stage and primary lesion size independently influenced the survival rates. Significant complications occurred in 9 patients (13%) and included necrosis (n = 4 patients), fistulae (n = 4 patients), and small bowel obstruction (n = 1 patient).

CONCLUSIONS. Interstitial irradiation can effect local control in the majority of patients with primary carcinoma of the vagina with acceptable morbidity. Long term cure is demonstrable in patients with Stage I–III disease. ***Cancer* 2001;91: 758–70.** © *2001 American Cancer Society.*

KEYWORDS: primary invasive vaginal carcinoma, radiation therapy, interstitial brachytherapy, local control.

"It has not been an uncommon occurrence that, when confronted with a rare clinical entity, I have found myself remarking to a colleague that perhaps 100 years must need pass before sufficient numbers have accumulated among various academics in order to allow the natural history of the disease and the efficacies of various treatment modalities to become discernible amidst a fog of obscurity. If prudence permits, I may go further and hold that such comments are not unique to my clinic and that similar words have been exchanged

among physicians the world over when a disease of exceedingly low incidence has been encountered which taxes our mental faculties."

Primary vaginal carcinoma was described first by Cruveilhier in 1827, when he addressed the Anatomical Society of Paris.[1] For nearly 70 years, there was no effective treatment for patients with this rare disease. In the 1890s, Fenger and Olshausen independently attempted to extirpate the lesion surgically.[2,3] In 1900, Ernst Wertheim applied his radical operation for cervical carcinoma to primary vaginal carcinoma and reported 5-year survival in only 2 of 11 patients.[4] In 1923, Holland,[5] Stevens,[6] and Dougal[7] each presented a patient who underwent the Wertheim procedure, but the follow-ups were brief.

For patients with lesions beyond superficial Stage I disease, the ability to obtain satisfactory surgical margins often is predicated on sacrificing the bladder and/or the rectum. Indeed, following Alexander Brunschwig's description of exenterative surgery for patients with gynecologic malignancies in 1948, vaginal carcinoma was rendered resectable through multivisceral sacrifice, although perioperative mortality and morbidity were significant.[8] For this reason, radiotherapy has played a predominant role in the management of patients with primary vaginal carcinoma.

The principles of radiotherapy derive from the discovery of the X-ray, for which German physicist Wilhelm Conrad Roentgen received the first Nobel Prize in Physics in 1901. A member of a French family of scientists, Madame Marie Sklodowska Curie, was awarded the Nobel Prize in Physics in 1903 for her work on radioactivity. Finally, the Scottish-American scientist Alexander Graham Bell suggested using radium in internal cancer therapy to a physician friend in 1903, 27 years after he demonstrated the first telephone apparatus.[9]

Radiation treatment for patients with vaginal carcinoma was reported first by Taussig in 1929 at the Barnard Free Skin and Cancer Clinic in Boston.[10] Of 18 patients, only 2 survived for more than 5 years. Addressing the Clinical Congress of the American College of Surgeons on 17 October 1934, he stated that "primary cancer of the vagina is very rare and almost universally fatal. We acknowledge our total inability to do anything effective." In 1934, Joe Vincent Meigs acknowledged that carcinoma of the vagina is a very serious disease, the treatment of which must be carefully planned and administered whether through irradiation, radical surgery, or a combination of the two modalities.[11]

External radiation may be integrated with brachytherapy to treat regional lymph nodes or subclinical extension of disease. Intracavitary applicators generally are designed to place a line of radioactive sources lengthwise within the vagina. However, due to inherent depth-dose limitations, intracavitary techniques are less suitable for patients with lesions measuring > 0.5 cm in depth in whom underdosing may be a consequence if normal mucosal tolerance is to be respected.

TABLE 1
Early Vaginal Carcinoma Series

Author	Period	No.	5-Year survival (%)
Wolf[12]	1918–1927	40	2.5
Moench[13]	1915–1930	41	17.0
Philipp and Gornick[a]	1913–1919	83	15.7
Healy and Brown[15]	1933	99	21.2
Masson[16]	1910–1927	80	22.5
Berven and Heyman[a]	1921–1936	58	10.4
Way[11]	1932–1948[b]	44	18.1
Livingstone[17]	1925–1940	76	10.5
Huber[18]	1922–1949	104	17.0
Messelt[19]	1932–1945	78	22.7
Bivens[20]	1931–1950	40	27.5
Palmer and Biback[9]	1919–1952	75	32.0
Smith[21]	1927–1946	109	12.8
Murphy[22]	1919–1949	103	23.3
Whelton and Kottmeier[23]	1930–1955	117	26.5
Murphy and Bozzini[24]	1919–1955	161	27.0
Latourette and Lourie[25]	1940–1959	256	28.0
Dunn and Napier[26]	1938–1960	40	42.5
Rutledge[27]	1941–1961[c]	43	35.0
Frick et al.[28]	1930–1966	42	35.7
Herbst et al.[29]	1927–1963	68	22.0

[a] Cited by Courtial report.[14]

[b] The range was not stated in the report but has been calculated from the tenth William Blair Bell Memorial Lecture delivered by Dr. Way before the Royal College of Obstetricians and Gynaecologists on 23 January 1948.

[c] The range was not stated in the report but has been calculated based on Dr. Rutledge's statement that the patients in the study presented over a 20-year period and that, for 43 patients, there has been a minimum follow-up of 5 years.

Data from early primary vaginal carcinoma series containing at least 40 patients from 1929 through the 1960s have been recorded in Table 1.[9,11–29] Five-year survival rates of 20–30% for all stages generally were achieved. Among the higher cure rates are Felix Noah Rutledge's series of 43 women who were treated at the M. D. Anderson Hospital and Tumor Institute in Houston (5-year survival rate, 35%)[27] and Dunn and Napier's account of 40 patients who were treated at the University of Iowa Hospitals (5-year survival rate, 42.5%).[26] Although large numbers of patients in these early series were treated with radiotherapy, surgery also was actively employed. In addition, many of the external beam and intracavitary devices used are now considered obsolete. With advancements in the field of radiobiology and improved methods and apparatus

through which radiation can be delivered, more long term cures have been achieved. Recently, Creasman et al.[30] reported on the National Cancer Data Base Report on carcinoma of the vagina: Among 4885 cases submitted from 1985 to 1994, the relative survival rates at 5 years for patients with International Federation of Gynecology and Obstetrics (FIGO) Stage I, II, and III–IV carcinoma were 73%, 58%, and 36%, respectively.

Afterloading interstitial brachytherapy was developed to improve target volume coverage and thereby to allow effective and homogeneous delivery of radiation in differing situations. Designed in the 1970s, the Syed-Neblett template insures optimal spacing and stability of the implant needles while allowing individualization of the extent of implant coverage.[31] The ease of its use and adaptability to different clinical scenarios represent the hallmarks of the technique.[32–36] The Syed-Neblett template procedure as applied to our vaginal carcinoma treatment program was last reported in 1983.[37] The experience has been updated and enlarged to better assess the efficacy and morbidity of the technique.

MATERIALS AND METHODS

Patients who were treated from 1976 to 1997 at the Women's Hospital of Memorial Medical Center in Long Beach, California and at the University of California, Irvine–Medical Center in Orange, California were identified through procurement of the Tumor Registry abstracts and review of the Radiation Oncology log books. The names were cross referenced with files from the Radiation Oncology, Pathology, and Epidemiology Departments as well as with files from the Gynecologic Oncology Division. The criteria of the League of Nations Committee (origin of the tumor in the vagina, cervix intact, and no evidence of extravaginal primary malignancy) were fulfilled in all patients, and all tumors were staged according to the Perez modification of the FIGO clinical staging system for patients with primary vaginal carcinoma. The Radiation Therapy Oncology Group toxicity criteria for the grading of complications were used. In addition to biopsy confirmation of vaginal carcinoma, all patients underwent detailed pelvic examination, cystoscopy, proctosigmoidoscopy or barium enema, computed axial tomography of the pelvis and abdomen, and chest radiography.

Summary of Radiotherapy

When feasible, external beam radiotherapy was administered prior to interstitial irradiation with a linear accelerator (n = 61 patients; 86%). Using anterior and posterior parallel and opposed portals encompassing the entire length of the vagina and pelvic sidewalls, radiation generally was delivered over a 28-day period at a dose of 1.8 grays (Gy) per day, 5 days per week, for a mean dose of 50.4 Gy. A midline block was placed in the anterior and posterior fields during the latter part of the treatment to limit the bladder and rectal doses to 40 Gy. When tumor extended to the lower one-third of the vagina, the inguinal lymph node regions were included electively in the treatment field.

In our treatment program, we held the dose of external beam radiotherapy constant at 50.4 Gy to reduce the size of the primary tumor without excessive morbidity. The interstitial dose was adjusted based on the stage of disease, tumor volume, and extent of infiltration and ranged from 16.5 Gy to 22 Gy (minimum tumor dose, 20 Gy).

All 71 patients with vaginal carcinoma were treated with interstitial brachytherapy (Fig. 1). Using a transperineal Syed-Neblett lucite dedicated vaginal template, the majority of the implants were created employing epidural analgesia. Multiple, 17-gauge, stainless-steel guide needles were inserted through the template and into the tumor-bearing regions of the vagina and lateral tissues. The implants were individualized with respect to the number of guide needles and depth of insertion.

X-ray localization films with inactive dummy sources were obtained next, followed by computerized dose distribution plotting and volume analysis using the ROC Program Module (Fig. 2). The placement of radioopaque contrast material in the rectum and Foley catheter balloon permitted calculation of the radiation dose that would be received by the rectum and bladder. Radioactive iridium-192 (^{192}Ir) seeds, spaced 1 cm apart in plastic ribbons, were afterloaded into the guide needles and left in place for a mean interval of 42 hours. The prescription dose of minimum radiation was given to the perimetry of implanted volume. Regions within the implanted volume that were encompassed by the isodose curves received a higher dose of radiation.

Seventeen patients received interstitial brachytherapy in conjunction with a laparotomy, which permitted the size and extent of the disease to be determined more precisely. There were no patients with extensive carcinomatosis that was discovered at the time of laparotomy, which would have necessitated aborting the "open" implant procedure in patients who underwent treatment with this technique for vaginal carcinoma. Bowel and bladder adhesions to the tumor were separated surgically, and the guide needles were placed through the perineal template into the entire lesion under direct vision and palpation. An omental pedicle graft was always interposed between

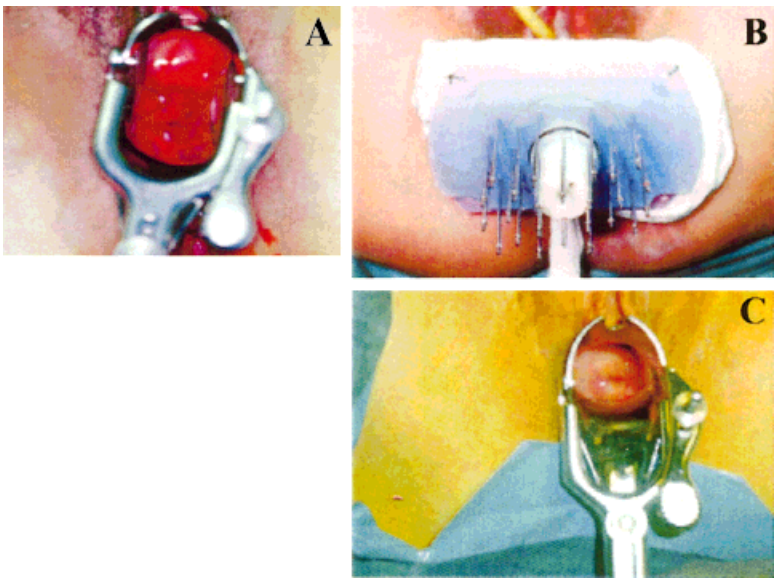

FIGURE 1. Treatment of a primary vaginal tumor using interstitial brachytherapy. (A) An International Federation of Gynecology and Obstetrics (Perez modification) Stage IIA squamous cell carcinoma of the vagina from a patient age 65 years; the friable lesion measured 3 cm in greatest dimension and completely obscured a normal uterine cervix. (B) After completion of a prescribed course of external beam radiotherapy, the first of two afterloading interstitial iridium-192 implants is created with 24 stainless-steel, hollow-guide needles placed directly into the tumor and secured using the Syed-Neblett dedicated plastic vaginal template. (C) A complete and sustained response to the radiotherapy program is achieved; the normal cervix is now visible at the proximal end of the vaginal cylinder.

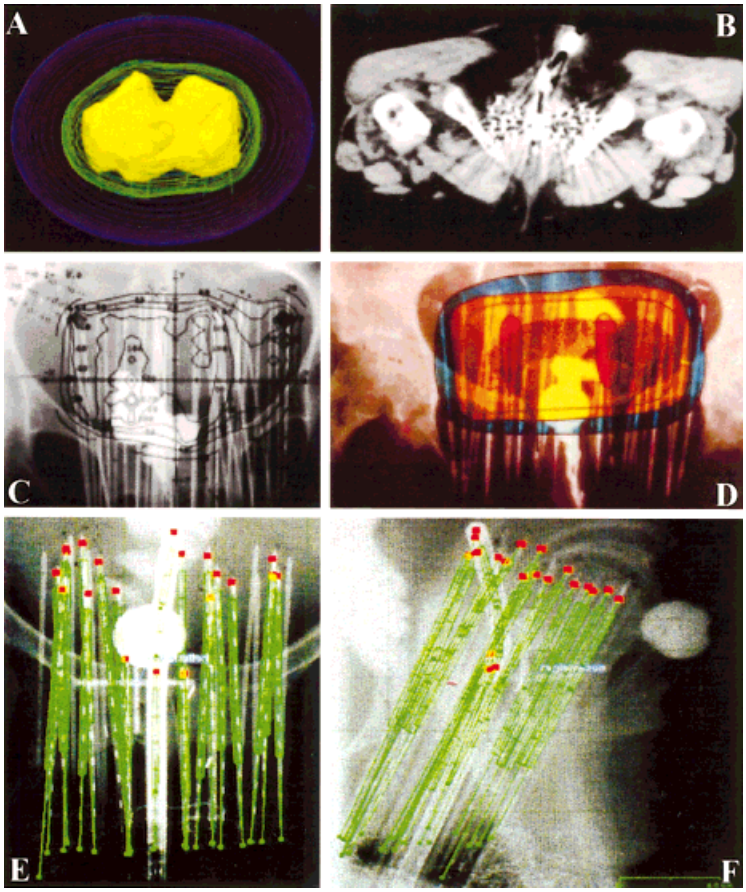

FIGURE 2. Radiographic localization films used in the development of the interstitial implant. (A) Computer-generated dimensions of the tumor to be implanted. (B) Computed axial tomography image of the pelvis in cross section revealing the presence of the needle tips. (C) X-ray localization of the interstitial implant with computer-generated dosimetry overlaid in blue outlines the radiation dose prescribed to the perimeter. (D) X-ray localization film demonstrating the position of the needles in the pelvis. (E,F) Anterior and lateral films following afterloading of iridium 192 isotope into the hollow-guide needles; contrast material in the Foley catheter balloon and in the rectum is demonstrable in both images, allowing for a calculation of the maximal exposure to the bladder and rectum, respectively.

the tumor and organs, such as the bladder and rectum, that may have been mobilized during the dissection. The omental pedicle graft also served to prevent small bowel loops from adhering to the implant site and provided a new blood supply to the area to be irradiated. Marker seeds were used to facilitate dosimetry planning and optimal needle placement of a second implant procedure (see below). This "open implant" approach was adopted in the later years of the study period.[38,39] To deliver an optimal total dose of

TABLE 2
Patient Characteristics

Characteristic	% (no.)
Study population (no.)	71
Median age in yrs (range)	59 (16–86)
Ethnicity (%)	
Caucasian (no.)	82 (58)
Hispanic (no.)	11 (8)
Other (no.)	7 (5)
History	
Hysterectomy	34 (24)
Pelvic malignancy	24 (17)
Pelvic radiotherapy	11 (8)
VAIN III	7 (5)
DES exposure	6 (4)
Symptoms	
Bleeding	53 (38)
Other	26 (18)
None	21 (15)

DES: diethylstilbestrol.

TABLE 3
Tumor Profiles

Characteristic	%	No.
Mean greatest tumor dimension		
(cm) (range)	3.2 (0.5–8.0)	48
Not recorded	—	23
Perez modification of FIGO stage		
I	14	10
IIA	20	14
IIB	35	25
III	21	15
IV	10	7
Location		
Apex	46	33
Middle and distal	54	38 (total)
Cell type		
Squamous	82	58
Adenocarcinoma	11	7
Clear cell carcinoma	7	5
Adenosquamous	1.4	1
Nuclear grade		
1	16	11
2	35	25
3	29	21
Unknown	20	14

FIGO: International Federation of Gynecology and Obstetrics.

interstitial radiation, a second implant procedure was performed 3 weeks after the first implant using the "closed" transperineal approach described above.

Statistical Analysis

Statistical methods employed for survival analysis included Kaplan–Meier life table analysis and nonparametric univariate linear rank statistics using Statistical Analysis Systems software (version 7; SAS Institute Inc., Cary, NC). A P value ≤ 0.05 was selected to represent statistical significance. The survival rate was adjusted for cause of death from vaginal carcinoma and was calculated at 2 years, 5 years, and 10 years.

RESULTS

From 1976 to 1997, 71 women underwent treatment for primary vaginal carcinoma at Memorial Medical Center of Long Beach and the University of California, Irvine-Medical Center and comprise the clinical material for this study (Table 2). The median age was 59 years, and 82% of the patients (n = 58) were Caucasian. One-third of the patients (n = 24) had previously undergone abdominal hysterectomy, most for a diagnosis of prior pelvic carcinoma (cervix, n = 15 patients; endometrium, n = 1 patient; anal carcinoma, n = 1 patient). All prior pelvic malignancies were diagnosed beyond 5 years prior to the diagnosis of vaginal carcinoma. Eight of these patients had also received postoperative adjuvant radiotherapy as part of the treatment program for cervical carcinoma. Five women (7%) and four women (6%) had a history of VAIN III and diethylstilbestrol (DES) exposure, respectively.

A little over 50% of the study population presented with vaginal bleeding, whereas 26% presented with vaginal pain or dysperunia, and 20% of the women were asymptomatic, having been diagnosed by vaginal biopsy of a suspicious lesion discovered during routine pelvic examination.

The mean greatest tumor dimension among patients in this series appears to have been 3.2 cm, with a range from 0.5 cm to 8 cm for the 48 patients in whom the primary lesion size was recorded. The stage distribution according to the Perez modification of the FIGO system has been recorded in Table 3 and included 20% for Stage IIA and 35% for Stage IIB; 14% of the patients presented with Stage I lesions, whereas 31% of the women had advanced (Stage III and IV) disease. The tumors arose and were confined to the vaginal vault in 46% of patients. The predominant cell type was squamous cell carcinoma (82%), but adenocarcinoma, clear cell carcinoma, and adenosquamous carcinoma also were observed. Of five women with clear cell carcinoma, four had had a documented history of in utero DES exposure. The vast majority of the lesions demonstrated an intracellular architecture consistent with a nuclear grade of 2.

Sixty-one women (86%) received external beam

radiotherapy as part of their treatment for primary vaginal carcinoma. This includes 60 previously unirradiated patients as well as 1 previously radiated patient who showed very minimal evidence of radiation change from two decades previously when she was treated for a cervical tumor.

Three patients received systemic therapy for radiosensitizing purposes. In two patients this consisted of intravenous cisplatin and, in one patient, oral hydroxurea.

For 22 of 47 women who had a uterus and apical vaginal lesions, the interstitial implant was developed using both ^{192}Ir seeds and a cesium-137 intrauterine tandem. In this fashion, the brachytherapy technique was similar to the treatment program we apply to patients with locally advanced, surgically unresectable cervical carcinoma. Seventeen women, as stated above, received their first interstitial implant in conjunction with a laparotomy; this was performed during the later years of the study period (1991–1997) and included women who had previously undergone hysterectomy as well as young women with clear cell carcinoma in whom ovarian preservation with surgical transposition was desirable.

The breakdown of the types of interstitial implants (i.e., open vs. closed, with or without teletherapy) as a function of disease stage along with additional details of the radiotherapy program appear in Table 4. The minimum tumor dose administered per implant was 20 Gy, with the total dose reaching 80 Gy when brachytherapy was integrated with external beam radiation therapy. The average bladder and rectum doses were 70 Gy and 65 Gy, respectively. For those patients who had a history of previous external pelvic irradiation, the minimum tumor dose prescribed was 60–70 Gy and was delivered through two interstitial implants only.

TABLE 4
Treatment Program

Treatment	%	No.
EBRT	86	61
Adjuvant systemic therapy	4	3
Interstitial brachytherapy		
^{192}Ir implant and ^{137}Cs tandem	31	22
^{192}Ir implant alone	69	49
^{192}Ir implant, closed and alone		
Stage		
I	—	2
IIA	—	4
IIB	—	3
III	—	—
IV	—	1
Total	—	10
^{192}Ir implant, closed and EBRT		
Stage		
I	—	8
IIA	—	3
IIB	—	13
III	—	15
IV	—	6
Total	—	44
^{192}Ir implant, open and EBRT		
Stage		
I	—	1
IIA	—	7
IIB	—	7
III	—	2
IV	—	—
Total	—	17
Total ^{192}Ir implant	—	71
Dosimetry (grays)		
Minimum tumor dose per implant	—	20
Implant and EBRT	—	80
Bladder	—	70
Rectum	—	65

EBRT: external beam radiotherapy; ^{192}Ir: iridium-192; ^{137}Cs: cesium-137.

Response and Survival

The actuarial local control rate for the study population was 75% (n = 53 patients). Of the patients with local failure (i.e., persistent disease and locoregional disease recurrence), 2 patients had disease that was confined to the vagina and/or pelvis, and 12 patients had disease that was associated with distant metastases. One of these patients with Stage I disease was rescued through the employment of an abdominal radical vaginectomy; the remaining 17 women who failed locally all succumbed to progressive disease. Finally, none of 11 women who failed at distant sites alone was salvageable.

The median follow-up has been 66 months, with a range from 15 months to 163 months. The 2-year, 5-year, and 10-year actuarial disease free survival rates are 73%, 58%, and 58%, respectively (Fig. 3). The actuarial 5-year survival rates by disease stage have been recorded in Table 5. Each of the 10 women with Stage I disease are alive at 5 years of follow-up. In addition, for patients with Stage IIA and IIB disease, a 60–61% 5-year survival rate was achieved; 30% of the women with Stage III disease have been cured. Finally, none of the seven patients with Stage IV lesions are alive at 5 years of follow-up.

The FIGO stage of disease, as modified by Perez (IIA–IV), and tumor volume (< 3 cm maximum dimension vs. > 3 cm maximum dimension) independently influenced both the ability to achieve local control and overall survival ($P < 0.05$). Prior pelvic

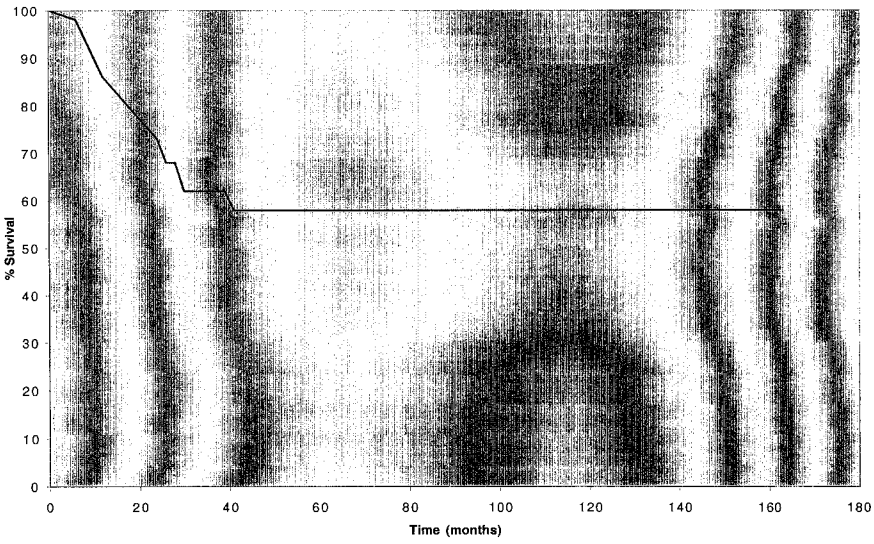

FIGURE 3. Overall actuarial disease free survival for the study population.

radiotherapy, antecedent malignancy, and previous hysterectomy did not have an independent statistical impact on either outcome measure.

Sequelae of Therapy

The severe complication rate for this series has been calculated at 12.7% (Table 6). The majority of these complications occurred in women who were treated with the "closed" implant technique (78%) and/or in women with a history of prior hysterectomy (66%). There was 1 patient with small bowel obstruction secondary to a radiation stricture that required surgical management. There were four patients with radionecrosis, including one that occurred in a women who had received previous pelvic radiotherapy. Finally, there were three instances of vesicovaginal fistula in women with Stage III disease and, one patient with rectovaginal fistula. Unfortunately, one of the women who developed a vesicovaginal fistula succumbed to urosepsis and constitutes the single treatment-related death in this series.

DISCUSSION

The optimal treatment methods for patients with vaginal carcinoma have been the subject of considerable investigation during the 20th century. Clearly, the relative rarity of these lesions has meant that the accumulation of experience in their treatment has been slow. Because the tumors may arise anywhere along the vaginal cylinder, therapy must be individualized, resulting often in a paucity of homogeneous treatment programs. An added problem is that the FIGO staging system does not incorporate tumor volume. There obviously are differences in treatment planning when considering patients with very small Stage I lesions or

TABLE 5
Local Control and Survival

Characteristic	No.
Median months of follow-up (range)	66 mos (15–163)
Local control rate (no.)	75% (53)
Failure to achieve CR and recurrences	
Local/pelvis alone (no.)	
Stage I	1
Stage IIA	—
Stage IIB	2
Stage III	3
Stage 4	—
Total	6
Local/pelvis and distant (no.)	
Stage I	—
Stage IIA	2
Stage IIB	4
Stage III	4
Stage IV	2
Total	12
Distant alone	
Stage I	—
Stage IIA	2
Stage IIB	2
Stage III	2
Stage IV	5
Total	11
Actuarial survival, overall (yrs)	
2	73%
5	58%
10	58%
Actuarial 5-yr survival by stage	
Stage I	100%
Stage IIA	60%
Stage IIB	61%
Stage III	30%
Stage IV	0%

CR: complete response.

TABLE 6
Major Morbidity

Severe complication	Implant	Disease stage	Prior history
Small bowel obstruction	Closed	IIA	Hysterectomy
Necrosis	Closed	IIB	Radiotherapy
Necrosis	Closed	IIB	Hysterectomy
Necrosis	Closed	IIB	Hysterectomy
Necrosis	Open	IIB	Hysterectomy
Rectovaginal fistula	Open	IIA	Hysterectomy
Vesicovaginal fistula	Closed	III	Hysterectomy
Vesicovaginal fistula	Closed	III	—
Vesicovaginal fistula[a]	Closed	III	—

[a] This patient developed urosepsis and died.

with Stage I lesions that involve the entire cylinder. Similarly, tumor volume and extensions play important roles in therapeutic considerations for patients with Stage II and III disease.

Similar to patients with cervical carcinoma, patients with primary vaginal carcinoma are amenable to early diagnosis, when the chances for cure are greatest. Unfortunately, most series have reported lower cure rates and substantially higher complication rates for patients with vaginal carcinoma compared with patients with similar stages of cervical carcinoma. This is predicated on the special anatomic and physiologic characteristics of the vagina. Early local spread is a consequence of the thin vaginal wall and absence of a dense facial investiture. In addition, depending on the location of the lesion, the rich anastomosing lymphatic channels may drain to pelvic or inguinal lymph node chains, mandating that each of these regions is considered in treatment planning. Finally, the apposition of the vagina to the bladder and rectum limits treatment options and leads to considerable visceral toxicity if anterior and/or posterior exenterative surgery is required. Anterior wall lesions may necessitate resection of the symphysis pubis, whereas posterior wall lesions are mirror images of rectosigmoid carcinomas for which the treatment of choice is an abdominal perineal resection.

Thus, radiotherapy has become the treatment of choice for patients with vaginal carcinoma, the techniques of which are protean. In 1963, Chau[40] described the radiotherapeutic strategies of the M. D. Anderson Hospital and Tumor Institute, where the methods emphasized the use of the Bloedorn applicator, volume radium needle interstitial implants, as well as supplemental external radiation therapy. Vaginal ovoids alone or in conjunction with cylinder or cone therapy were employed for patients with superficial lesions of the vagina, whereas patients with more infiltrative tumors received radium implantation with an open-bladder strategy. The presence of a uterus permitted the use of uterine tandem and ovoids. The Fletcher–Suit afterloading tandem and ovoids as well as the Delclos afterloading vaginal irradiation applicator and enhanced computerized dosimentry planning are examples of increasing sophistication through which modern results have approached the treatment of patients with carcinoma of the cervix or endometrium. Rutledge[27] observed in 1967 that, compared with the surface application of intravaginal radium therapy, the interstitial radium needles permitted the delivery of a higher dose of irradiation to the immediate tumor-bearing tissue and at a greater depth. He noted, however, that the dosimetry of interstitial brachytherapy is complicated and requires sophisticated calculations to ensure the delivery of a homogeneous dose to the bulk of tumor-containing tissue without producing tissue necrosis.

A number of investigators have examined their institutional experiences retrospectively over the past several decades and concluded that the improved results appear largely to be a reflection of individualization of isotopic implantation in conjunction with external beam radiotherapy. For example, in 1979, Pride et al.[41] observed that the survival rate from invasive squamous cell carcinoma of the vagina had improved significantly over the past 25 years and suggested that this was due to the widespread use of interstitial irradiation of the local vaginal tumor and administration of supravoltage radiation. These ideas are best observed when comparing the crude survival rates from reports of patients who were treated predominantly during the first half of the 20th century (20–30% 5-year survivorship for all stages; Table 1)[9,11–29] with patients who were treated during the latter half of the 20th century (the two- to five-year survivorship for patients with Stage II–III disease was 30–70%; Table 7).[41–56] Series selected for tabulation in the latter table were those in which a minimum of 25 patients had been treated with radiotherapy for primary vaginal carcinoma (data from the current study are entered on the last line of Table 7).

Prempree and colleagues[42] reported the experience of the Martha V. Filbert Radiation Center of the University of Maryland Hospital in 1977. Those investigators based their program on the M. D. Anderson model described by Brown et al. in 1971[57] in which improved survival had been credited to properly integrated irradiation therapy combining interstitial and intracavitary radium with external beam radiotherapy. Thus, for Prempree and coworker's study population of 58 women with locally advanced disease, radiotherapy principally consisted of supervoltage external ir-

TABLE 7
Modern Radiotherapy for Patients with Primary Vaginal Carcinoma

Author	Stage II	Stage III	Stage IV	% Complications[a]
Pride et al.[41] (1956–1971) (no.)	IIA: 6; IIB: 16	4	8	18.6
% LF	IIA: 33; IIB: 68.8	75	100	—
% 5YS	IIA: 66; IIB: 31	25	0	—
Prempree et al.[42] (1957–1975) (no.)	IIA: 20; IIB: 11	20	7	8.4
% LF	IIA: 15; IIB: 18	30	86	—
% 5YS	IIA: 65; IIB: 63.5	40	0	—
Chu et al.[51] (1958–1979) (no.)	IIA: 14; IIB: 5	14	12	11
% LF	IIA + IIB: 32	43	100	—
% 5YS	IIA: 51; IIB: 24	35	0	—
Rubin et al.[52] (1958–1980) (no.)	35	14	12	13
% LF	11	21	58	—
% 5YS	48	54	0	—
Dancuart et al.[44] (1955–1982) (no.)	42	38	11	12
% LF	14	24	27	—
% 5YS[b]	55	37	0	—
Kucera and Vaura[48] (1975–1984) (no.)	23	46	25	6.4
% LF	21.7	19.6	36	—
% 5YS	43.5	34.8	16.7	—
Perez et al.[43] (1953–1984) (no.)	IIA: 49; IIB: 26	16	8	12
% LF	IIA: 39; IIB: 46.1	37.5	75	—
% 10YS	IIA: 55; IIB: 43	32	0	—
Reddy et al.[53] (1965–1985) (no.)	22	6	1	18
% LF	14	83.3	100	—
% 5YS	71	0	0	—
Urbanski et al.[50] (1965–1988) (no.)	37	40	15	12.8
% LF (85% overall)	Not specified	Not specified	Not specified	—
% 5YS	54.1	22.5	0	—
Stock et al.[46] (1970–1988) (no.)	27	10	6	22.4
% LF	53	60	100	—
% 5YS	48	40	0	—
Dixit et al.[49] (1985–1989) (no.)	10	42	10	10
% LF	30	81	100	—
% 2YS	70	19	0	—
Lee et al.[54] (1964–1990) (no.)	IIA: 16; IIB: 10	10	6	12.3
% LF	IIA: 12; IIB: 32	20	33	—
% 5YS	IIA: 80; IIB: 39	79	62	—
Fine et al.[47] (1963–1991) (no.)	20	12	7	14.5
% LF	25	25	42.9	—
% 5YS	68	58	0	—
Ali et al.[55] (1969–1991) (no.)	21	4	2	10
% LF	42.9	50	100	—
% 5YS	53	50	0	—
Stock et al.[56] (1962–1992) (no.)	25	9	7	8.5
% LF (68% overall)	Not specified	100	Not specified	—
% 5YS	31	0	0	—
Current study (1976–1997) (no.)	IIA: 14; IIB: 25	15	7	12.7
% LF	IIA: 14; IIB: 24	47	28.6	—
% 5YS	IIA: 60; IIB: 61	30	0	—

% LF: % local failure; % 2YS, % 5YS, 10YS: 2-, 5-, and 10-year disease free survival rates.

[a] Severe morbidity including necrosis, fistulae, etc., for the entire study group (i.e., includes Stages I–IV).

[b] Survival data as reported by Fletcher et al. from the M. D. Anderson Hospital for 47 Stage II, 27 Stage III, and 6 Stage IV primary vaginal carcinoma patients who were treated from 1948–1972.[45] Survival data from M. D. Anderson Hospital not presented by Dancuart et al. in their report.[44]

radiation using ^{60}cobalt teletherapy followed by highly individualized internal irradiation using intracavitary applicators or interstitial implantation of ^{226}radium or ^{192}Ir isotopes. The local failure rates increased with FIGO Stage from 0% for patients with Stage I disease to 86% for patients with Stage IV disease. For all stages combined, the overall local failure rate was 24%, and the overall absolute disease free 5-year survival rate was 56.3%. Prempree et al. suggested that, when comparing their results with those from Perez and coworker's preliminary communication from Barnes Hospital[58] and the M. D. Anderson 1971 report,[57] there were comparable results among patients with Stage 0, Stage I, and Stage IIA disease. However, their results appeared to be superior for patients with Stage IIB and III disease, and they attributed this to the individualization of radium implantation. Although all three institutions used high dose pelvic external beam radiation to a dose of 4000 rads with a pelvic wall boost for patients with locally advanced disease, Prempree's team made considerably wider use of radium needle implantation to deliver high doses to the parametrial regions in these patients.

The principle of aggressive parametrial implantation was established subsequently for patients with carcinoma of the cervix[33] and has been developed further since in a presentation of 149 patients with vaginal carcinoma by Perez and colleagues in 1988.[43] In their long term analysis of patients who underwent interstitial or intracavitary brachytherapy with or without external beam radiotherapy at Mallinckrodt Institute of Radiology at the Washington University School of Medicine, the investigators stated that the dose of irradiation delivered to the primary tumor and the parametrial extension when present by brachytherapy techniques was critical in achieving durable local and pelvic control.

Turning back the to M. D. Anderson studies,[27,40,44,45] Dancuart and coworkers updated their experience in 1988 and presented a failures analysis of 162 women who were treated from 1955 to 1982 by the techniques cited above.[44] Although central (i.e., local) failures were observed in 14%, 24%, and 27% of patients with Stage II, III, and IVA disease, respectively (n = 91 patients; Table 7), a stratification of failures by treatment revealed that central failures occurred in 22% of patients who underwent external radiation alone and in 17–18% of patients who underwent brachytherapy alone or in conjunction with external therapy. When analyzing pelvic failures, a similar trend of increased central failure also was observed whenever brachytherapy had been omitted.

These conclusions were supported in 1992 by Stock and his team at the Memorial Sloan-Kettering Cancer Center in New York City.[46] They studied brachytherapy technique in 49 patients with primary vaginal carcinoma and observed a significant increase in 5-year actuarial survival for those patients who had brachytherapy as part of their treatment compared with patients who were treated with external beam irradiation alone (50% vs. 9%; $P < 0.001$). It is noteworthy that, for patients with locally advanced disease, there was an improvement in crude disease free survival with the use of ^{192}Ir interstitial brachytherapy compared with the use of intracavitary brachytherapy (75% vs. 44%; $P = 0.08$). Further testimony to the benefit derived through the incorporation of interstitial brachytherapy was provided by Fine and coworkers[47] in their 1996 analysis of 63 women who were treated at the Roswell Park Cancer Institute: Local failure rates of 25% for patients with Stage II and III disease were obtained, with overall 5-year survival rates of 68% and 58%, respectively.

There are three large modern experiences in which an intracavitary technique was used exclusively.[48–50] Writing from the University of Vienna in 1991, Kucera and Vavra[48] examined the outcomes of a subgroup of 110 patients who were treated predominantly with intracavitary radium and detected 1 local failure among 16 women with Stage I lesions; the local and pelvic failure rates increased as the disease stage progressed. Distant failures were identified only among women with advanced disease in whom local failure also was exhibited. Those authors state that their intracavitary approach was replaced in 1985 by a remote afterloading interstitial technique using high dose rate (HDR) iridium.

Dixit and colleagues from the Gujarat Cancer and Research Institute in Ahmedabad described three treatment strategies in their 1993 communication: external irradiation alone, external irradiation with a cesium-137 vaginal cylinder, or external irradiation with a cesium-137 vaginal cylinder and intrauterine tandem.[49] External irradiation alone yielded poor results, as expected. Furthermore, although they observed a 70% 2-year survival rate for Stage II patients, all 21 women with Stage III or IV disease had failed both locally as well as in the parametrium in under 24 months.

In 1996, Urbanski and coworkers recorded their experience at the Maria Sklodowska-Curie Memorial Institute in Kraków, where treatment also consisted primarily of intracavitary radium or cesium with or without external beam radiotherapy.[50] Although a failure analysis by stage was not presented, the overall locoregional failure rate was 85%. Those investigators suggested that the failure to incorporate interstitial implants into their treatment schedule may have contributed significantly to their low cure rate.

The treatment-related severe morbidity rates ranged from 6.4% to 22.4% (Table 7),[41–56] with our own study group observing a 12.7% incidence rate for severe radiotoxicity, which includes one treatment-related death. The complication rates recorded by the three groups in which intracavitary devices were used exclusively have ranged from a respectable 6.4% to an unsatisfactory 18%.[48–50]

Because there are no other large interstitial series reported for primary vaginal carcinoma, it is difficult to draw any definite conclusions regarding the toxicity. Whereas Martinez et al.[59] noted a 0% complication rate among 26 women with vaginal/urethral lesions who were treated with the Martinez Universal Perineal Interstitial Template technique, not all of the patients had primary vaginal carcinoma. In an earlier communication, Syed et al.[32] prepared guidelines that advocated the careful integration of external and interstitial irradiation and selective differential unloading to respect normal tissue tolerance and avoidance of dosimetric "hot spots."

In the current series, the association between previous hysterectomy and severe morbidity is noteworthy, because it was observed previously by Manetta et al.[60] at the Milton S. Hershey Medical Center at Pennsylvania State University: Five of their six patients who required surgical management of severe treatment-related morbidity had undergone a previous hysterectomy for benign gynecologic conditions. Furthermore, it is of considerable interest that, in four of our patients who had undergone a prior hysterectomy and subsequently developed a severe complication, the interstitial brachytherapy procedure had been performed before we had adopted the policy of administering the first implant in conjunction with a laparotomy in the posthysterectomy setting. This "open" implant technique also may be advisable for patients with bulky vaginal vault lesions as well as those large tumors in which the superior extent may be appreciated incompletely.

Because of the rarity of primary vaginal carcinoma, no prospective studies can be performed, and, when examining data from retrospective series, the possibility of treatment selection bias and differences in patient populations and radiotherapeutic technique renders it difficult to make meaningful comparisons. Nevertheless, some general observations may be drawn from the studies cited above. First and foremost, the need for brachytherapy is paramount, as evidenced by the poor survivorships reported in subsets of patients in which only external irradiation was utilized. Second, most groups have incorporated some method of interstitial technique to their program, especially for patients harboring lesions thicker than 0.5 cm; this is noteworthy, because it contrasts with the observation, that in most treatment centers, interstitial brachytherapy does not have a predominant role in the management of other gynecologic and pelvic malignancies. Finally, the need for aggressive parametrial isotopic implantation for women with locally advanced disease cannot be overemphasized.

For the reasons listed above, credence may be given to our report, because we have described a treatment program in which interstitial brachytherapy was employed in all patients, often with tailored external beam irradiation. In fact, ours is a pure interstitial brachytherapy experience with a consistency of technique and a respectable follow-up. Our previously reported overall long term survival rate of 56%[37] has essentially remained constant (i.e., 58% presently), with all recurrences occurring within 5 years. Thus, the plateau of the survival curve beyond 5 years indicates the presence of a cured population. Although it remains futile to draw generalizations and to make comparisons between our series and others, still, we have obtained some level of homogeneity in our treatment program that has been lacking in much of the past published experiences. However, despite having obtained respectable cure rates in patients with Stage II disease, we still find that local failure continues to be problematic for these patients. Furthermore, local failure developed in nearly 50% of patients with Stage III lesions, bringing the survival rate in that group down to 30% at 5 years. Given our extensive experience and uniform application of interstitial brachytherapy throughout the study period, we will continue to employ this radiotherapeutic modality in the settings of bulky disease, infiltrative disease, and in those patients with macroscopic residual tumor after completion of external beam radiotherapy.

Subclinical (i.e., microscopic) disease requires 50 Gy to prevent local recurrence; for macroscopic lesions (e.g., Stage I), a minimum of 60 Gy is required to avoid an unacceptable recurrence rate of 30% if therapy is stopped at 50 Gy. We feel that it is better to boost with interstitial brachytherapy, so that a smaller tumor volume may be managed with a lower dose in order to avoid the excessive morbidity that would be incurred using external beam radiotherapy alone. Even though our mean tumor size was 3.2 cm in greatest dimension, interstitial irradiation provided a superior dose distribution than what could have been achieved with intracavitary applicators, allowing a more conformed therapy.

In view of the satisfactory survival of patients with Stage I and II disease using radiotherapy, pelvic exenteration should be reserved for women with central Stage IV disease or with central disease recurrence

after undergoing radiotherapy. Conversely, women with advanced tumors with involvement of the bladder and/or rectum are potential candidates for a combination of preoperative pelvic irradiation and surgery, because radiation alone continues to produce poor results in these patients.

The need for improved local control may be depicted thematically and expounded on by the following two algorithms: 1) local failure → pelvic failure → distant failure → death from disease; and 2) local control + pelvic control + distant control = survival. Local control is critical in preventing disease progression; conversely, failure at any site (local, pelvic, or distant) results in patient demise.

Local control must remain a function of the individualization of interstitial brachytherapy through variations in the depth of needle insertion, position, spacing and pattern of the needles within the template, number of needles used, and number of radioactive sources afterloaded per needle. We are interested in determining whether local control may be enhanced further by using interstitial hyperthermia, the administration of chemotherapy as a radiosensitizing agent, and HDR interstitial applicators. The HDR systems may result in superior dose optimization, allowing for a smaller treatment volume and, hence, diminished morbidity.

Pelvic control may be predicated on tailored external beam radiotherapy, radiosensitizing chemotherapy, and the performance of the "open" implant technique as well as aggressive paramentrial implantation with iridium-192 needles and/or the utilization of an intrauterine cesium-137 tandem. Finally, distant control requires effective systemic therapy, which is not available at present.

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