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LONG-TERM RESULTS OF LOW-DOSE-RATE INTERSTITIAL–INTRACAVITARY BRACHYTHERAPY IN THE TREATMENT OF CARCINOMA OF THE CERVIX

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Purpose: Brachytherapy plays a major role in the treatment of patients with carcinoma of the cervix. However, routine intracavitary brachytherapy may not be feasible or adequate to treat locally advanced disease. The purpose of this retrospective study (spanning a 20-year period) was to determine the outcome of interstitial low-dose-rate brachytherapy in the treatment of bulky or locally advanced cervical cancer. The long-term survival and safety of this technique were evaluated, along with its impact on local and locoregional control, disease-free survival, and complications.
Methods and Materials: A total of 185 previously untreated patients with cervical cancer were treated between 1977 and 1997. According to the International Federation of Gynecology and Obstetrics classification, 21 patients had Stage IB (barrel), 77 Stage II, 77 Stage III, and 10 Stage IV disease. All patients were treated by a combination of external megavoltage irradiation to the pelvis to a dose of 5040 cGy followed by interstitial–intracavitary implants to a dose of 40–50 Gy to the implanted volume in two applications.
Results: Clinical local control was achieved in 152 (82%) of the 185 patients. A 5-year disease-free survival rate of 65%, 67%, 49%, and 17% was achieved for patients with Stage IB, II, III, and IV disease, respectively. Eighteen (10%) of the 185 patients developed Radiation Therapy Oncology Group Grade 3 or 4 late complications.
Conclusion: Patients with locally advanced cervical cancer, or with distorted anatomy, may be treated adequately with interstitial brachytherapy to achieve excellent locoregional control and a reasonable chance of cure with acceptable morbidity.   © 2002 Elsevier Science Inc.

Carcinoma of the cervix, Brachytherapy, Interstitial–intracavitary, Low dose rate.

INTRODUCTION

Cervical carcinoma is the 10th most common malignancy in the United States, with 12,800 new cases diagnosed and 4600 deaths in 2000 (1–3). The incidence and mortality rates of cervical carcinoma vary considerably throughout the world, with the highest observed in the developing countries (4). The combination of external beam radiotherapy (EBRT) and intracavitary brachytherapy (ICBT) is considered the standard of care, except in younger patients with early-stage disease. Many large series have reported 5-year disease-free survival (DFS) rates of 80–90% for Stage I, 55–70% for Stage II, 30–50% for Stage III, and 10–15% for Stage IV disease (5–12). Conventional ICBT with tandem and ovoids or ovoids alone may not deliver an adequate dose in cases of extensive and bulky tumors, obliterated fornices, lower vaginal involvement, and carcinoma of the cervical stump (13, 14).

Syed and others developed a technique of interstitial–intracavitary brachytherapy implantation to improve the

dose distribution in patients with locally advanced disease (15–18). Several authors, including Aristizabal *et al.* (19), Prempree (11), and others (20–22), have reported good results using similar techniques during the past two decades.

METHODS AND MATERIALS

The records of 203 patients with histologically proven carcinoma of the uterine cervix treated by low-dose-rate (LDR) interstitial brachytherapy were reviewed. All patients were treated at Long Beach Memorial Medical Center (Long Beach, CA) and California Hospital, Los Angeles (Los Angeles, CA) between June 1977 and August 1997. The indications for LDR interstitial brachytherapy for cervical cancer included carcinoma of cervical stump, bulky disease, poor vaginal anatomy (narrow vagina, obliterated vaginal fornices), extensive vaginal involvement, extensive parametrial and pelvic sidewall involvement, and poor tumor shrinkage after EBRT. Eighteen patients were excluded from the study because they refused to continue with the second interstitial implant and were considered to have incomplete treatment; thus, a total number of 185 patients were subjects of this study.

The pretreatment evaluation included history, physical examination, and examination under anesthesia (by both a gynecologist and a radiation oncologist), including cystoscopy and proctoscopy. The workup included complete blood counts, biochemical profile, and urine analysis. Radiographic studies included chest X-ray, i.v. pyelography, lymphangiography for the earlier patients, and CT of the pelvis and abdomen. Bone scans were done when clinically indicated. More than 50% of these patients were referred by radiation oncologists after having attempted unsuccessful conventional ICBT. Of the 185 patients, 46 (25%) underwent staging laparotomy; 64 (35%) had a pretreatment hemoglobin level of <10 g/100 mL; and 86 (47%) had a history of smoking.

Of the 185 patients, 161 (87%) had squamous cell carcinoma, 14 (8%) adenocarcinoma, 5 (2%) adenosquamous carcinoma, and 5 (3%) small cell carcinoma. Thirteen (7%) had well-differentiated, 61 (33%) moderately differentiated, and 111 (60%) poorly differentiated carcinoma. Other patient characteristics are presented in Table 1.

All patients were retrospectively staged according to the International Federation of Gynecology and Obstetrics (FIGO) staging system (23). Most patients had advanced stage disease (i.e., IIB-IIIB) (Table 2). These patients had the most unfavorable clinical and technical factors to be treated by conventional ICBT (i.e., 106 [68%] of 155 patients had bilateral parametrial involvement and 97 [53%] of 185 patients had tumors >6 cm; Tables 3 and 4). Of the 185 patients, 137 (74%) had their pelvic and para-aortic lymph node status evaluated. Sixty-six (48%) of 137 patients had pelvic or para-aortic lymph node involvement, proven by exploratory laparotomy (29 patients; 21%), needle biopsy (11 patients; 8%), or CT or MRI examination (26 patients; 19%; Table 5).

Table 1. Patient characteristics

Characteristic	n	%
Pathologic feature		
Squamous cell carcinoma	161	87
Adenocarcinoma	14	8
Adenosquamous carcinoma	5	3
Small cell carcinoma	5	3
Differentiation		
Well	13	7
Moderate	61	33
Poor	111	60
Size (cm)		
≤6	88	47
>6	97	53
Hemoglobin (mg/dL)		
≤10	64	35
>10	121	65
Cervical stump cancer	9	5
Hydronephrosis	16	9
Lower vaginal involvement	33	18

Treatment protocol

All patients were treated by megavoltage EBRT to the whole pelvis, with a median dose of 5040 cGy in a daily fraction of 180–200 cGy using either AP and PA opposed portals or a four-field box technique. A lower midline block of 4×10 cm^2 was used in 89% of the patients at 3960 cGy to shield the rectum and bladder. The interstitial-intracavitary brachytherapy procedure was performed 1–2 weeks after the completion of EBRT and the second procedure 2 weeks after the first. Twelve (7%) of the 185 patients underwent interstitial implantation at the time of exploratory laparotomy for staging. The technique of the interstitial brachytherapy procedure has been previously reported (15–18). In brief, the interstitial-intracavitary brachytherapy implant procedure is performed with an intrauterine tandem as in the conventional ICBT technique, but the intracavitary ovoids have been replaced with interstitial needles in the parametria (Fig. 1). The number of parametrial needles ranged from 16 to 38 (mean 29) to encompass the disease extension, with a mean of 7 seeds/ribbon (range 6–12). ^{137}Cs sources were used in the tandem and ^{192}Ir in the parametrial needles. Tandem could not be used in 144

Table 2. Clinical FIGO staging

FIGO stage	n	%
IB	21	11
IIA	9	5
IIB	68	37
IIIA	13	7
IIIB	64	35
IVA	8	4
IVB	2	1
Total	185	100

Abbreviation: FIGO = International Federation of Gynecology and Obstetrics.

Table 3. Parametrial involvement

FIGO stage	Total cases (n)	Unilateral cases (n)	Bilateral cases (n)
IIB	68	32	36 (53)
IIIA	13	3	7 (54)
IIIB	64	9	55 (86)
IVA	8	1	7 (87)
IVB	2	1	1 (50)
Total	155	46 (30)	106 (68)

Numbers in parentheses are percentages.

Table 5. Lymph node status

FIGO stage	Cases evaluated (n)	Negative (n)	Positive (n)
I	16	5	11 (69)
II	60	45	15 (25)
III	53	19	34 (64)
IV	8	2	6 (75)
Total	137	71 (52)	66 (48)

Numbers in parentheses are percentages.

(41%) of 349 applications (Table 6). For patients in whom tandem could not be used because of bulky tumor or distorted anatomy, it was replaced by 4–6 central needles. Typical doses delivered to the implanted volume varied according to the FIGO stage from 20 to 25 Gy per application. Because point A has traditionally been the prescription point for intracavitary applications, the dose rate to the "Manchester point A" was also calculated. Individualized dose distributions were obtained using the TP11/Theraplan V05 (MDS, Nordion, Canada) treatment planning system after reconstructing the implant from orthogonal films taken with coded-dummy trains. The dose rate to the bladder and rectal points reconstructed from the orthogonal films was also calculated. The dose rate to the medial parametrium (point A) ranged from 60 to 80 cGy/h, and the lateral parametrium (point B) received 50–80% of the dose to point A. The dose delivered to the lateral parametria was increased to one or both sides either by differential unloading of the tandem or by using higher activity ^{192}Ir sources in the lateral needles. The bladder and rectal dose was kept to <65% and <60% of the point A dose, respectively.

Of the 185 patients, 44 (24%) received one or more cycles of systemic chemotherapy at the primary gynecology oncologist's discretion. Twenty-three patients received neoadjuvant, 11 concurrent, and 10 patients post-RT chemotherapy. Cisplatinum was used as a single agent in 6 patients, 5-fluorouracil in 6, a combination of both in 20, and hydroxyurea in 12 patients. Forty-six (25%) of 185 patients with extensive disease also received interstitial radiofrequency hyperthermia with each implant for 45–60 min to

Table 4. Tumor size

FIGO stage	Tumor size (cm)				
	≤4	>4–6	>6–8	>8–10	>10–15
IB	3	15	2	1	0
IIA	1	7	1	0	0
IIB	6	36	18	8	0
IIIA	0	6	6	1	0
IIIB	1	11	24	19	9
IVA	1	1	2	1	3
IVB	0	0	0	0	2
Total	12 (6)	76 (41)	53 (29)	30 (16)	14 (8)

Numbers in parentheses are percentages.

41–43°C within 3 h of loading or unloading the radioactive sources.

All patients were examined by a radiation oncologist and gynecologic oncologist after irradiation completion, at 3-month intervals in the first year, 4-month intervals in the second year, every 6 months for up to 5 years, and yearly thereafter. The median follow-up of these patients was 51 months (range 3–223).

Statistical analysis

Statistical analyses of the data were based on standard survival analysis techniques. The DFS was calculated according to the Kaplan–Meier method (24), using the Statistical Package for the Social Sciences, version 9.0.1, software (SPSS, Chicago, IL). Patients were analyzed from the date of the implant to the date of the last follow-up visit, disease recurrence, or date of death. The aim of this study was to evaluate the long-term results and safety of this technique, along with its impact on locoregional control (LRC), DFS, and complications, and to determine the factors that influence the outcome.

Local control was defined as total resolution of clinically visible and/or palpable tumor of the cervix. LRC was defined as no evidence of disease in the area of the original tumor (i.e., cervix, vagina, and parametria) by clinical examination and imaging studies. Overall survival was calculated as the time from the date of implant to the last follow-up or death from any cause. DFS was calculated from the date of implant to LRC, distant metastasis, or cancer-related deaths.

RESULTS

Despite the unfavorable prognostic and technical factors in this group of patients, local control in 152 (82%) of 185 patients was achieved. However, after a median follow-up of 51 months (range 3–223), 136 patients (73%) had LRC until the time of death or last follow-up. In contrast, of the 18 patients who were excluded from the analysis because they failed to complete the planned treatment, only 34% achieved LRC.
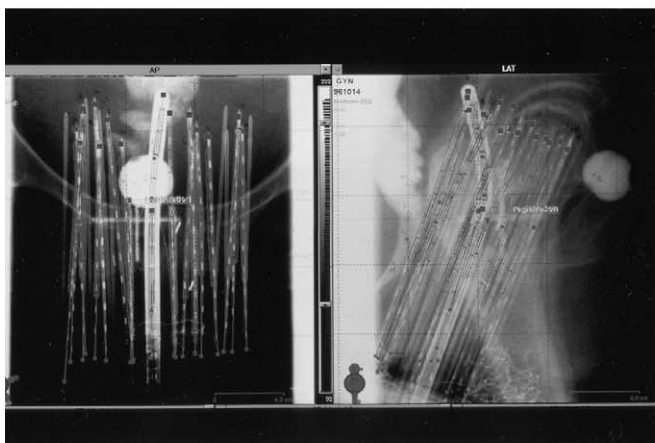
According to the FIGO stage, a LRC rate of 71% was achieved for patients with Stage IB, 89% with IIA, 79% with IIB, 92% with IIIA, 61% with IIIB, 75% with IVA, and 100% with IVB. Seventy-two (82%) of the 88 patients with
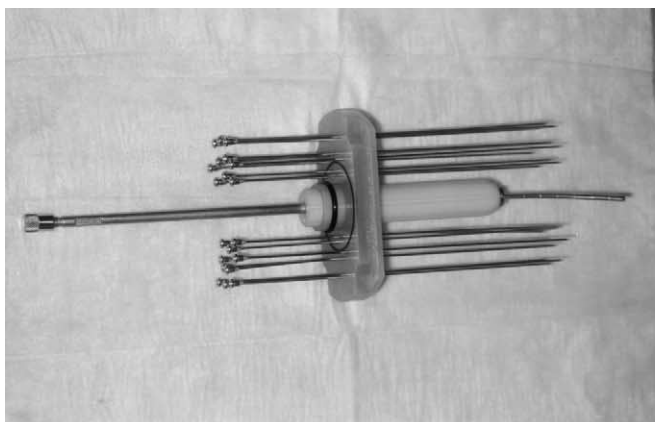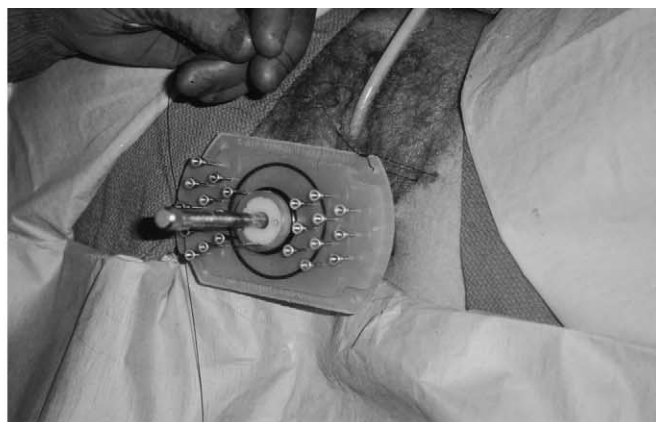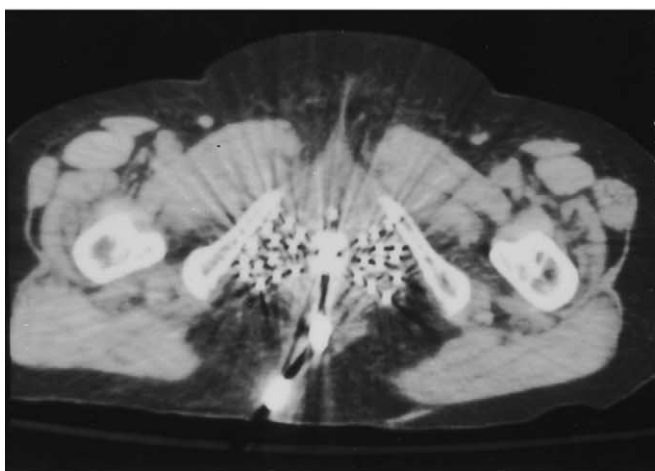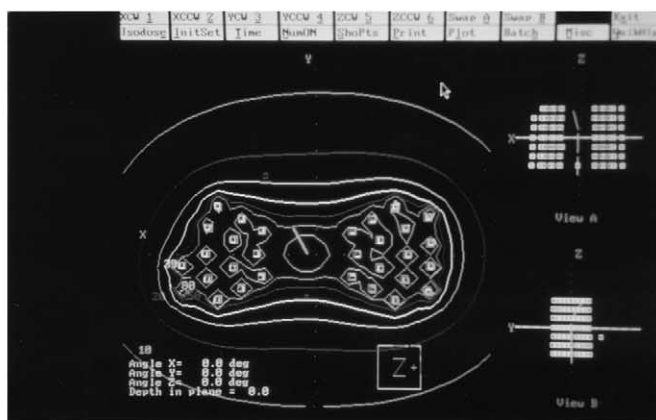
Fig. 1. Carcinoma of the cervix, implant technique. (a) Assembled Syed–Neblett template. (b) Implant procedure completed. (c) X-ray localization films. (d) Computerized dose distribution overlay on AP film. (e) CT localization films. (f) Cross section with computerized dose distribution plotting.

tumor <6 cm achieved LRC, and 64 (66%) of 97 patients with tumor >6 cm had LRC. Patients with a low level of hemoglobin before treatment were transfused to a minimum of 10 g/100 mL; however, there was still an obvious difference in LRC, 55% vs. 83%, for patients with an initial

hemoglobin level <10 g/100 mL vs. >10 g/100 mL, respectively ($p = 0.0001$). For the 66 patients with known positive lymph nodes, LRC was observed in 39 (59%) of 66 patients vs. 63 (89%) of 71 with negative nodal status. In the 48 patients with unknown lymph node status, LRC was

Table 6. Intracavitary tandem application

FIGO stage	Patients (n)	Applications without tandem (n)	Applications with tandem (n)
I	21	10	26
II	77	48	100
III	77	71	74
IV	10	15	5
Total	185	144 (41)	205 (59)

Numbers in parentheses are percentages.

achieved in 34 (71%). When we correlated the history of smoking with LRC, we found that a higher LRC rate was achieved in the nonsmokers than in the smokers (69 [82%] of 84 vs. 57 [67%] of 85). Although patients treated with hyperthermia had a higher LRC rate (77% vs. 60%), it had no impact on overall survival. Among the 62 patients who underwent chemotherapy, 41 (66%) had LRC vs. 95 (77%) of the 123 without chemotherapy.

Seventy-seven (42%) of 185 patients developed treatment failure (i.e., 49 [27%] with locoregional and 28 [15%] with distant metastasis only). Sixteen of the 49 patients with locoregional failure also had distant metastasis. The pattern of locoregional failure was central in 12%, parametrial recurrence with no evidence of central disease in 9%, and central and parametrial recurrence in 6%. The highest in-field failure was observed in patients with Stage IIIB (25 [39%] of 64).

The 5-year DFS rate for the entire group of patients was 58% (Fig. 2). According to the disease stage, a 5-year DFS of 65%, 67%, 49%, and 17% was achieved for those with Stage I, II, III, and IV, respectively (Fig. 3). No treatment-related mortality occurred.

According to the five different tumor sizes, the 5-year DFS rate was 13% for patients with tumors >10 cm, 54% for those >8–10 cm, 63% for those >6–8 cm, 59% for those >4–6 cm, and 73% for those with tumor ≤4 cm. The difference was statistically significant between tumors ≤4
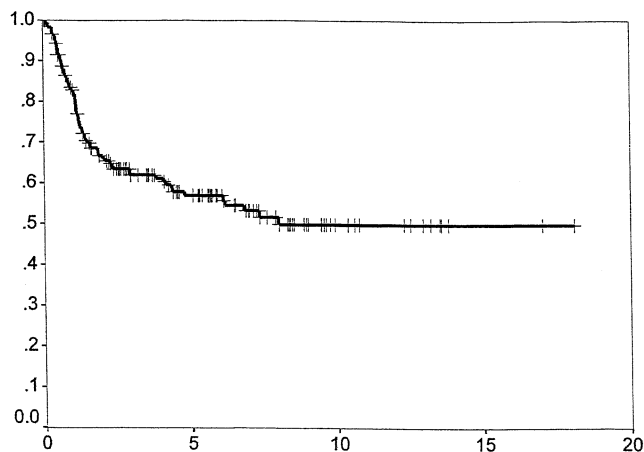
cm, >4–6 cm, and >6–8 cm vs. tumors >10 cm (p = 0.001, 0.002, and 0.0004, respectively; Fig. 4). The lymph node status had a significant impact on the DFS rate; it was 74% with negative lymph nodes and 36% with metastatic lymph nodes. No major difference was found in the 5-year DFS rate between well and moderately differentiated tumors (69% vs. 67%). However, patients with poorly differentiated tumors had a 50% rate of 5-year DFS (Fig. 5). The difference in the 5-year DFS rate was dramatic (30% vs. 71%) for patients with an initial hemoglobin level <10 g/100 mL vs. >10 g/100 mL (p = 0.0001; Fig. 6).

The prognostic value of patients aged ≤70 vs. >70, clinical FIGO stage, chemotherapy use, and history of smoking were investigated for their influence on DFS. The patients >70 years had a 74% DFS rate vs. 54% for those <70 years. The patients who received chemotherapy had a DFS rate of 37% vs. 65% for those without chemotherapy. On univariate analysis, age, chemotherapy, and stage were significant, with p values of 0.017, 0.002, and 0.021, respectively. However, only chemotherapy remained significant by multivariate analysis p = 0.036). The patients with no history of smoking had a 65% DFS rate vs. 48% for smokers. This was significant on both univariate and multivariate analysis (p = 0.03 and 0.02, respectively).

Complications

Acute reactions. Most patients experienced transient symptoms of acute cystourethritis and proctitis (Grade 1 toxicity), according to the Radiation Therapy Oncology Group (RTOG) criteria. However, 48 (24%) of 185 patients developed Grade 2 early proctitis, and 14% Grade 2 cystitis. These symptoms resolved in all patients within 4–6 weeks after completion of the treatment with conservative management.

Late reactions. According to the RTOG/European Organization for Research and Treatment of Cancer late radiation morbidity scoring scheme, 5 (3%) of 185 patients developed Grade 2 late bladder complications with moderate frequency of urination and 12 patients (6%) developed Grade 2 proctitis with moderate diarrhea. All these patients responded to conservative management. Three (2%) of 185 patients developed Grade 3 bladder complications with severe frequency and hematuria. No Grade 4 bladder complications were encountered. Fifteen patients (8%) developed late Grade 3 and 4 gastrointestinal complications (8 [4%] with bowel obstruction and 7 [4%] with fistula formation). Most of these complications occurred in patients (7 [47%] of 15) who had undergone prior surgical intervention. Among the 8 patients who had bowel obstruction, 1 patient had received para-aortic lymph node irradiation, another patient had undergone permanent iodine implantation for ovarian metastasis, and 3 had had prior surgical intervention and required colostomy. In 3 patients with fistula, it occurred in the early experience as a result of the tandem having slipped down and the ^{137}Ce source remaining in the upper vagina. This was corrected in later patients by pushing the tandem into the uterus after completion of the

Fig. 2. Kaplan-Meier DFS curve for the entire group.
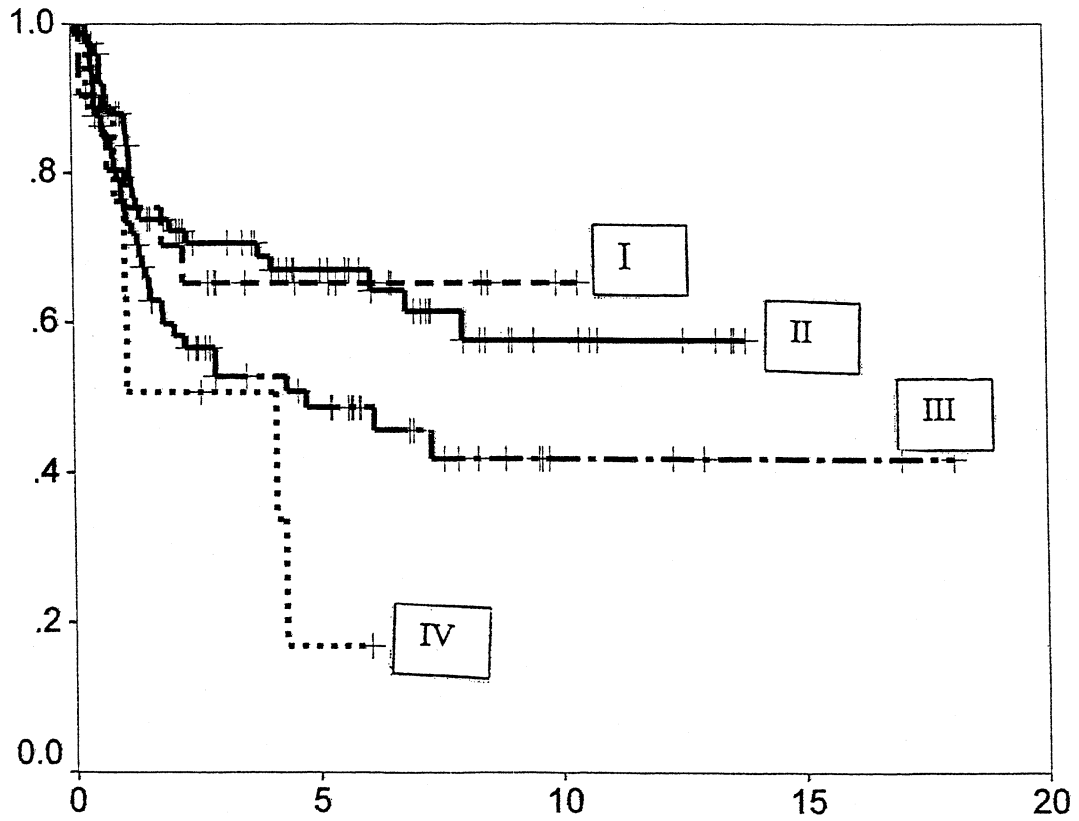
Fig. 3. Kaplan-Meier DFS by stage.

procedure. Two of 7 patients had fistulas as a result of persistent or recurrent disease. Five of these 7 patients had Stage IIIB disease. Six patients required colostomies; however only 1 was left with a permanent colostomy (Table 7).

DISCUSSION

Brachytherapy is an essential component in the treatment of carcinoma of the uterine cervix, in addition to EBRT.
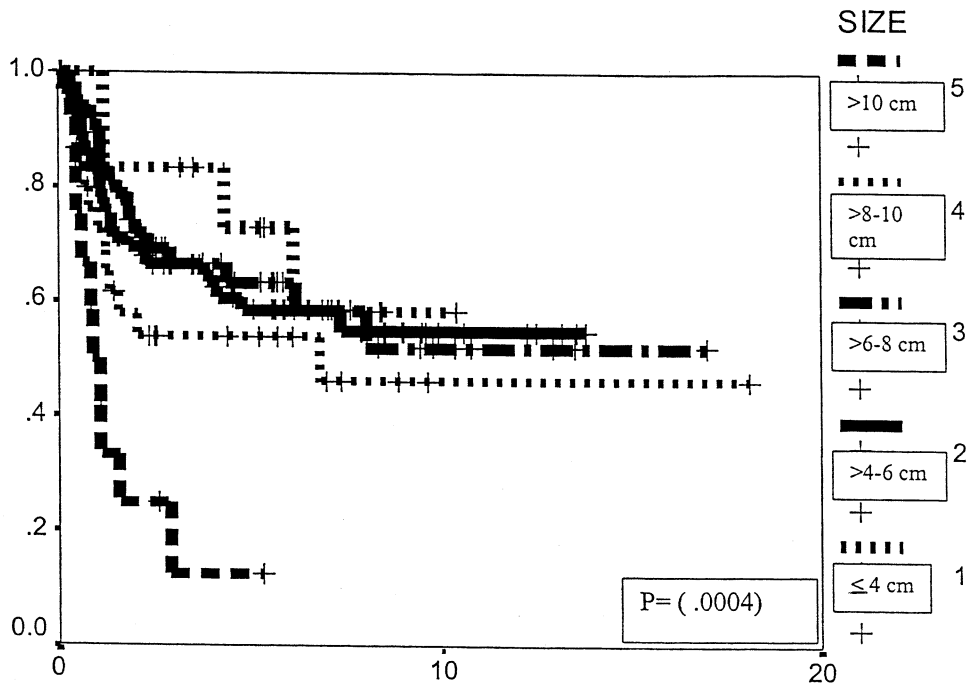

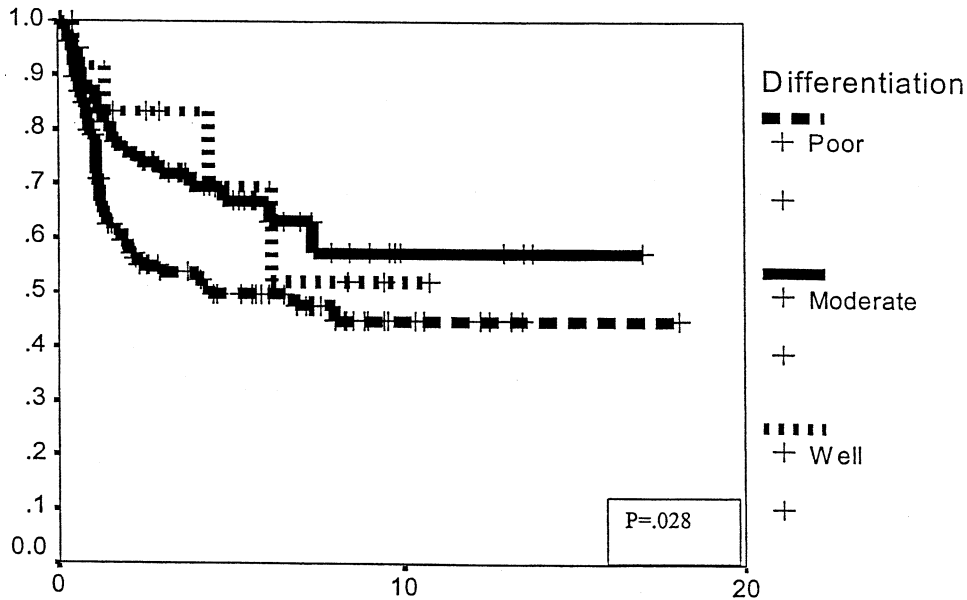Fig. 4. Kaplan-Meier DFS by tumor sizes.

Fig. 5. Kaplan-Meier DFS by tumor differentiation.

Brachytherapy has the advantage of delivering a maximal dose to the tumor and minimal dose to the surrounding structures (i.e., bladder and rectum). The treatment results of locally advanced cervical cancer remain poor with EBRT and conventional ICBT (5–12). Although ICBT is adequate for relatively early-stage cervical cancer (i.e., IB and IIA), it does not deliver the optimal dose for patients with bulky and locally advanced carcinoma of the cervix, in patients with early disease but with distorted anatomy, or when tandem cannot be used. Local control rates with conventional irradiation (EBRT and ICBT) range from 88% to 92% for Stage I, 66% to 88% for Stage II, 48% to 63% for Stage III, and only 13% to 18% for Stage IV disease (9, 25–32). These

results point to the fact that local control is poor for locally advanced cervical cancer (28, 33, 34). In 1995, a patterns-of-care study for carcinoma of the uterine cervix reported an "actuarial in field failure" rate of 24–35% for Stage II and 31–63% for Stage III disease at 5 years (6). The variability between the different reports may have been due to the wide range of tumor volume even in the same stage of the disease, as well as the lymph node status, which are not considered in the clinical FIGO staging system. Unfavorable tumor biology may also provide more reasons for the high failure rates.

The strong positive correlation between LRC and survival requires improvement in the radiotherapeutic tech-
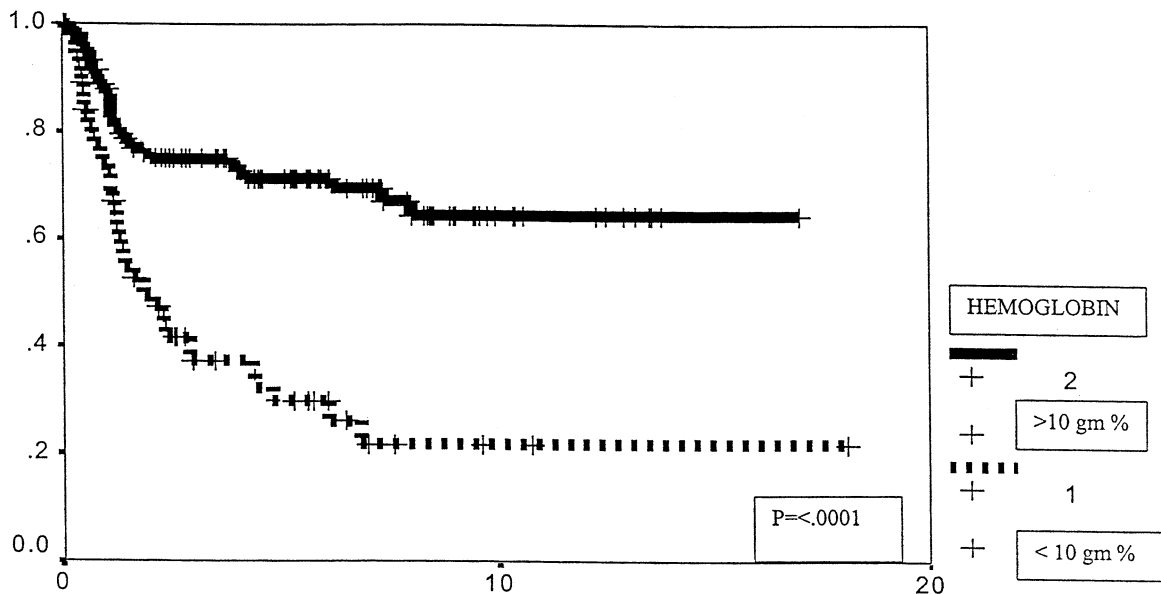

Fig. 6. Kaplan-Meier DFS by hemoglobin level.

Table 7. RTOG late Grade 2, 3, and 4 toxicity

FIGO stage	Patients (n)	Grade 2 (n)		Grade 3 (n)		Grade 4 bowel fistula formation	
		Bladder	Bowel	Bladder	Bowel*	RV	RV+VV
I	21	0	0	0	0	0	0
II	77	1	5	0	2	2	0
III	77	3	7	3	5	4	0
IV	10	1	0	0	1	0	1
Total	185	5 (3)	12 (6)	3 (2)	8 (4)	6 (3)	1 (1)

* Bowel obstruction.
Abbreviations: RTOG = Radiation Therapy Oncology Group; FIGO = International Federation of Gynecology and Obstetrics; RV = rectovaginal; VV = vesicovaginal.
Numbers in parentheses are percentages.

niques for locally advanced carcinoma of the cervix. Interstitial–intracavitary LDR brachytherapy was designed to tailor the treatment to the tumor volume to improve the LRC in patients with unfavorable tumor profiles, for which conventional ICBT fails to deliver adequate doses. In the late 1940s, Waterman et al. (35) reported a 31% 5-year survival rate in patients with Stage IIIB disease using a transvaginal radium needle implant technique; however, the rate of severe complications was 14% (36). In 1978 and 1983, Prempree and Scott (11, 37) reported a 78% local control rate for Stage III carcinoma of the cervix using the same technique. In 1977, we published the details of an after-loading interstitial-intracavitary implant technique (15). In 1986, the details of the technique, modifications, and treatment outcome were published (17). Since then, several investigators have published their treatment results using the same techniques during the past 20 years. Unfortunately, only 6% of the patients with gynecologic malignancies in the United States are treated with this technique according to the survey conducted by the American Brachytherapy Society (20).

Landoni et al. (38), in 1997, reported a survival rate of 72% for patients with bulky Stage IB disease treated with radiotherapy. In our present series, the DFS rate for those with Stage IB carcinoma of the cervix was lower than for those with Stage IIB (65% vs. 67%) because 86% of the patients with Stage IB disease had tumors >4 cm in diameter and 52% had pelvic and 25% para-aortic lymph node metastasis.

Monk et al. (39) reported a survival rate of 21% and 29%, respectively, for Stage IIB and IIIB carcinoma of the cervix, with a complication rate of 21% using LDR interstitial brachytherapy. However, these patients received much lower doses of brachytherapy compared with patients receiving conventional intracavitary irradiation for similar disease stages. Local control was better when the tumor dose was higher than "4000 mg-hr." Syed and Feder (15) and Aristizabal et al. (19) reported a 68% and 77% DFS rate, respectively, for similar stages. Several other authors (11, 16, 19, 21, 22, 39–49) have reported their results, which are summarized in Table 8. The wide variation in the

results and complication rates may be related to differences in technique, dosimetry, and treatment planning systems and the total dose delivered.

The patients treated in our series with Stage IIIB carcinoma of the cervix had much worse prognostic factors (i.e., large tumors, extensive parametrial involvement, ureteral obstruction, and an inability to use the tandem) in 41% of applications. Hughes-Davis et al. (22) had shown a 36% 3-year DFS rate for patients in whom tandem and ovoids were used vs. 18% for those for whom the tandem could not be used in Stage IIB and IIIB carcinoma of the cervix. In our data, with interstitial-intracavitary LDR brachytherapy, the patients with Stage IIIB who had worse prognostic factors compared favorably with those reported by Eifel (50) (49% vs. 53% 5-year DFS rate).

Tumor size and its anatomic extensions are fundamental predictive prognostic factors for carcinoma of the cervix in all stages of the disease and should be evaluated carefully in choosing the type of brachytherapy (26, 32, 50–54). Most investigators correlated tumor size and stage with the 5-year survival (5–12). Bulky tumor was defined as >6 cm (32, 55). Patients with bulky tumors are the most susceptible to central recurrence (56). Nag et al. (48), in 1998, reported a 24% actuarial local control rate using interstitial brachytherapy for implanted volumes >6 cm in largest diameter and 51% for implanted volumes <6 cm (p = 0.02). In our present series, even though 53% of the patients had a tumor >6 cm, an excellent LRC rate of 73% was achieved. The 5-year DFS rate was 63% in patients with 6–8-cm tumors, and only 13% for those with tumors of >10 cm (p = 0.0004).

The hemoglobin level has been known to be an independent and highly significant predictive and prognostic factor in patients with carcinoma of the cervix (55). Many studies have demonstrated a correlation between patients' hemoglobin level and LRC (52, 54, 56–58). A small, randomized, prospective study from Princess Margaret Hospital concluded that blood transfusions improved pelvic disease control (57). Girinsky et al. found a significant correlation between prognosis and hemoglobin level before and during radiotherapy (58). Our present series using the Kaplan-

Table 8. Literature series for low-dose-rate interstitial radiation

LDR series	Published year	FIGO stage	*n*	CR (%)	LC (%)	LRC (%)	DFS (%)	Serious complications (*n*)	Follow-up (y)
Feder *et al.* (16)	1978	III–IVA	38	—	—	—	60*	—	1.3–3.3
Tak (40)	1978	IB–IVA	24	79	—	—	67	4	1–7
Gaddis *et al.* (41)	1983	IB–IVA	75	100	—	70	59	21	<1–5
Ampuero *et al.* (42)	1983	IB–IVA	21	85	59	—	43	24	2–3.4
Prempree *et al.* (37)	1983	IIB	49	84	—	—	65	8	5
Aristizabal *et al.* (43)	1983	IA–IVA	26	—	85	—	—	33	1–4
Martinez *et al.* (21)	1984	IIB–IIIB	37	84	—	83	57	5	1–7.5
Aristizabal *et al.* (19)	1986	IIB	45	100	—	—	77†	9	5
Syed *et al.* (17)	1986	IB–IVA	60	78	—	78	58 (50)*	3	5
Erickson *et al.* (44)	1989	I–IV	—	—	74	—	—	—	—
Bloss *et al.* (45)	1992	IIB–IIIB	25	72	—	—	64	4	2
Rush *et al.* (46)	1992	IIB–IIIB	5	100	—	—	40	20	1.7
Fontanesi *et al.* (47)	1993	I–IV	—	—	87	—	60	20	<1–7
Hughes-Davies *et al.* (22)	1995	IIB–IIIB	49	68	25	—	32	12–20	3
Monk *et al.* (39)	1997	IIA–IVA	70	61	31	—	24 (29)*	21	5
Nag *et al.* (48)	1998	IB–IVA	31	—	48	—	25	3	1–5.5
Gupta *et al.* (49)	1999	—	—	78	60	—	55	3–24	4.7
Present series	2001	IB–IVB	185	87	82	73	57 (49)*	9	<1–18.6

Abbreviations: LDR = low dose rate; FIGO = International Federation of Gynecology and Obstetrics; CR = complete response; LC = local control; LRC = locoregional control; DFS = disease-free survival.

* Stage IIIB.

† Actuarial.

Meier survival analysis, confirmed that the patients with hemoglobin >10 g/100 mL had a significantly higher 5-year DFS rate (71%) than did patients with hemoglobin <10 g/100 mL (30%; *p* = 0.0001). LRC seemed to be significantly better statistically in nonsmokers than in smokers (82% vs. 67%, *p* = 0.02).

Although we have improved LRC in patients with locally advanced disease using interstitial-intracavitary brachytherapy; however, 44 patients (24%) still died of distant metastasis. The high rate of distant metastasis in these patients despite the aggressive pelvic radiation encouraged us to use systemic chemotherapy. Many randomized and nonrandomized trials have used concurrent chemotherapy with irradiation, improving LRC and DFS. Cisplatinum-based chemotherapy with radiation yielded a complete clinical response rate of 60–85% in patients with advanced disease (59–61). Concurrent chemotherapy and pelvic irradiation has become the standard in the treatment of locally advanced carcinoma of the cervix. Five recently completed prospective randomized trials have shown a survival benefit for cisplatin-based chemotherapy given concurrently with radiotherapy (62–67). These trials included patients with Stage IB2–IV disease. These studies have demonstrated a significant survival benefit for this combined modality, with a decreased risk of death by 30–50%. Although our study was not randomized, the patients who received chemotherapy did worse than the patients who did not (37% vs. 65%). This may have been because the those patients who had worse disease received chemotherapy. Furthermore, most of these patients (19 of 44) received non–cisplatinum-based chemotherapy (i.e., hydroxyurea and 5-fluorouracil). Thirty-three patients received chemotherapy nonconcurrently (i.e., 23 neoadjuvant

and 10 after irradiation). This is the least effective regimen, as shown by the results of our study and as reported by other authors (68, 69).

According to RTOG criteria, serious late complications (Grade 3 and 4) occurred in 10% of patients. These data compare favorably with other published data, which range from 4% to 24% (Table 7). However, our LRC was significantly better than that reported after conventional ICBT for similar stage disease. Ten of 17 patients who developed major late complications received their treatment during the developmental phase of this treatment protocol.

In LDR implants with limited seed strengths along the needle length, it is imperative that the active length be about 15% longer than the target length. Specifying the desired dose at the basal dose points as defined by the Paris system does not yield satisfactory results, because the Paris System does not address either larger volume implants or the source-line configuration of concentric circles as defined by the templates we used. By loading peripheral needles with nearly double the strength over the central sources, dose homogeneity in the order of ±10% is achievable in the entire implanted volume when only needles were used. However, if an intrauterine tandem is also used, the dose in the cervical area is at least 50% more than the prescribed dose. Recently, we have switched to CT-based treatment planning in which reconstruction of the implant is carried out from the CT data. Relatively uniform dose distributions are aimed throughout the target volume. In the transverse sections, a reference isodose line covers the peripheral needles with a margin of about 3 mm. With dose optimization, which helps reduce the dose to the surrounding critical structures while covering the target volume with a relatively

uniform dose, the outcome is expected to be improved further, with reduced morbidity.

CONCLUSIONS

The combination of EBRT and interstitial–intracavitary brachytherapy in the treatment of locally advanced carcinoma of the cervix is safe and well tolerated with acceptable morbidity. We achieved a 73% overall LRC rate and a 58% 5-year DFS rate in patients with locally advanced disease and unfavorable prognostic factors, with only 10% Grade 3 and 4 late complications. Interstitial–intracavitary brachytherapy has the following advantages: It delivers optimal doses to the tumor volume irrespective of the anatomic distortions and delivers high doses to the lateral parametria without significant increase in the doses to the rectum and bladder by using differential activity or differential unloading. This technique is the most suitable in patients with locally advanced disease with bulky tumor, parametrial and lower vaginal involvement, early disease but distorted anat-

omy or a narrow vagina, or carcinoma of the cervical stump. Tumors >6 cm, poorly differentiated tumors, positive lymph nodes, hemoglobin level <10 g/100 mL, and smoking are significant negative prognostic factors for both tumor control and DFS. The development of advanced CT-based computer treatment planning systems may further reduce the morbidity. However, despite remarkable LRC with interstitial brachytherapy, the problem of distant metastasis remains unresolved. Concurrent cisplatinum-based chemotherapy with irradiation has been shown, in various randomized trials, to improve LRC and DFS. For the past 5 years, we have been using concurrent chemotherapy with irradiation. We believe that adequate training of radiation and gynecologic oncologists in the field of interstitial implantation is desirable and would, it is hoped, achieve better treatment results for cervical cancer, especially in certain indications, as described above. Since 1996, LDR has been replaced by HDR brachytherapy in our institution for patients with carcinoma of the cervix. The details and results of this technique will be separately published.

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