ELSEVIER

Brachytherapy 5 (2006) 49–55

BRACHYTHERAPY

Low-dose-rate vs. high-dose-rate intracavitary brachytherapy for carcinoma of the cervix: The University of Alabama at Birmingham (UAB) experience•

Elizabeth Falkenberg[1], Robert Y. Kim[1,*], Sreelatha Meleth[2], Jennifer De Los Santos[1], Sharon Spencer[1]

[1]*Department of Radiation Oncology, University of Alabama at Birmingham, Birmingham, AL*
[2]*Department of Biostatistics, University of Alabama at Birmingham, Birmingham, AL*

ABSTRACT

PURPOSE: To review the clinical outcome retrospectively of cervical cancer patients treated definitively with either high-dose-rate (HDR) or low-dose-rate (LDR) brachytherapy.

METHODS AND MATERIALS: One hundred sixty patients (44 Stage I, 83 Stage II, and 33 Stage III) were treated from 1990 to 2000 with curative intent for carcinoma of the cervix. One hundred three LDR patients were compared to 57 HDR patients. Two groups were treated during the same period. An external beam dose of 45 Gy to the entire pelvis was delivered at 1.8 Gy per fraction to most patients before the first intracavitary insertion in both groups. Brachytherapy was delivered in one to two LDR implants or four to five HDR implants at 6 Gy per fraction. The prescribed dose to Point A for LDR was at least 80–85 Gy. Patient characteristics were similar for each cohort. Point A doses were similar for each stage. The primary endpoints assessed were survivals and failure sites. Endpoints were estimated using the Kaplan–Meier method and comparisons between treatment groups were performed using the log-rank test.

RESULTS: The median followup was 48 months for the LDR group and 59 months for the HDR group. For all stages combined and stage for stage in both groups, there was no statistically significant difference in locoregional control, cause-specific survival, and overall survival for LDR compared with HDR. Locoregional control and overall survival were 78% and 60% for LDR compared to 76% and 55% for HDR at 3 years, respectively ($p = 0.96$ and $p = 0.48$). Median cause-specific survival values for LDR vs. HDR were 71 and 81 months, respectively ($p = 0.62$). The cause-specific survival for LDR patients was 62% compared with 59% for HDR patients at 3 years. For Stage IB2, II, and III LDR patients, cause-specific survival rates were 62%, 67%, and 45%, compared to 67%, 57%, and 33% for HDR at 3 years, respectively ($p = 0.75$, $p = 0.95$, and $p = 0.48$). For patients with a recorded site of first failure, the most common site was locoregional (56%) and then distant metastases (26%). Eight patients who were cancer free developed late complications requiring surgical intervention. Two patients were in the HDR group (3.5%) and 5 in the LDR group (4.8%).

CONCLUSIONS: Similar outcome was observed for LDR compared with HDR intracavitary brachytherapy for the entire cohort. In this review, HDR group was not inferior to LDR group in advanced stages. This is likely because our patients were treated with brachytherapy after a high dose of external pelvic radiotherapy in both LDR and HDR patients.

Keywords: Low-dose-rate; High-dose-rate; Brachytherapy; Cervical cancer; External beam radiation

Received 9 December 2005; received in revised form 15 December 2005; accepted 15 December 2005.

• Note: Presented at the annual meeting of the American Society for Therapeutic and Radiation Oncology, in Salt Lake City, UT in October 2003.

* Corresponding author. Department of Radiation Oncology, University of Alabama at Birmingham, 130 TI, 1824 6th Avenue South, Birmingham, AL 35249. Tel.: +1-205-975-0222; fax: +1-205-975-0784.

E-mail address: rkim@uabmc.edu (R.Y. Kim).

1538-4721/06/$ – see front matter
doi:10.1016/j.brachy.2005.12.001

Introduction

Since Margaret Cleaves (1) first performed intracavitary brachytherapy for cancer of the cervix in 1903, the radiation therapy of cervical cancer has traditionally been based on low-dose-rate (LDR) intracavitary brachytherapy. Recent technical advances in high-dose-rate (HDR) brachytherapy offer the opportunity for individualized dosimetry, outpatient treatment, and elimination of radiation exposure of medical personnel. Although HDR brachytherapy has been used successfully for more than 30 years in Asia and Europe, its use has been relatively low in the United States (2).

Historically, HDR brachytherapy was first applied to cervical cancer by Henschke *et al.* (3) and O'Connell *et al.* (4) in the early 1960s. In 1972, Joslin *et al.* (5) reported their experience with HDR brachytherapy for cervical cancer. Since that time, a number of clinical studies confirmed the equivalence in pelvic control and overall survival between LDR and HDR (6). However, most of these trials are retrospective studies compared with historical controls. There are a few single-institution studies that directly compared LDR with HDR brachytherapy in the literature (7–10). There are now four single-institution published randomized trials comparing LDR to HDR brachytherapy (11–14).

Our objective of this report is to evaluate clinical outcome of cervical cancer patients treated at the University of Alabama at Birmingham (UAB) with either LDR or HDR brachytherapy within the same period of time.

Methods and materials

Patient population

One hundred sixty patients with carcinoma of the cervix (44 Stage IB, 83 Stage II, 33 Stage III) were treated with curative intent using a combination of external beam radiotherapy and intracavitary brachytherapy from January 1990 through December 2000: 103 patients were treated with LDR and 57 patients were treated with HDR brachytherapy. Twenty-eight additional patients treated during this same period were excluded based on Stage IV disease or surgically staged positive para-aortics nodes.

Routine clinical staging was jointly performed by a gynecologic oncologist and a radiation oncologist according to the International Federation of Gynecology and Obstetrics (FIGO) staging system. Work-up included chest x-ray, CT of the abdomen and pelvis, and complete blood count with metabolic profile. Patient characteristics were similar for each cohort (Table 1). Median age for HDR patients was 58.5 years compared to 57 years for LDR patients, and 93% of patients had squamous cell carcinoma. Karnofsky performance status (KPS) was 80% or greater for most patients. Overall, 53% of patients were African Americans and 46% were Caucasians.

Table 1
Patient characteristics for LDR and HDR

	LDR		HDR	
	Number of patients	%	Number of patients	%
Patient number	103		57	
Histology				
Squamous	94	91	55	96
Adenocarcinoma	7	7	1	<2
Adenosquamous	0	0	1	<2
Other	2	2	0	0
Age: median	57		58.5	
KPS >80%[a]	72	86	43	93
Race				
Caucasian	46	45	27	49
African American	55	54	28	51
Stage				
IB1	7	7	4	7
IB2	13	13	20	35
II	58	58	25	44
III	25	25	8	14

[a] KPS values not available in 30 patients.

External pelvic radiation

An external beam dose of 45 Gy to the entire pelvis was delivered at 1.8 Gy per fraction using anterior–posterior (AP) and posterior–anterior (PA) opposing fields or a four-field box technique before the first intracavitary insertion to the majority of the patients in both HDR and LDR groups: median dose 45 Gy (ranging 19.8–54.0 Gy) for HDR and median dose 45 Gy (ranging 0–57.6 Gy) for LDR. External beam irradiation was delivered using conventional radiographic simulation and CT simulation (since 1997) for treatment planning. The upper border for the pelvis box field was placed at L4–L5 and the lower border was 2–3 cm beyond the lowest extent of the tumor. The lateral borders were 2 cm lateral to the bony pelvic brim. For the lateral fields, the upper and lower borders were identical to the AP/PA fields. The anterior border of the lateral field was placed anterior to the pubic symphysis with at least 2.0-cm margin around the uterus. The posterior border of the lateral field was placed at the level between S2 and S3 with at least 2.0-cm margin around gross tumor by CT scan. Treatments were given with 15-MV photons and prescribed to the isocenter at midplane. A parametrial boost was delivered between each LDR and HDR implant using a 4-cm-wide central shield or a custom block while also reducing the upper field border to the bottom of the sacroiliac joints to bring the dose to 55–60 Gy at Point B.

HDR and LDR brachytherapy

In all patients, the intracavitary doses were prescribed to Point A, which was defined as 2 cm cephalad and 2 cm lateral to the cervical os along the plane of the tandem. In the HDR group, we use either 4 or 5 brachytherapy delivered at 6 Gy depending on the size of the tumor (Table 2). The linear-quadratic formula was used to calculate the LDR dose-equivalent contribution to Point A for the HDR treatments.

Table 2
Current HDR fraction schedules at UAB for cervical cancer

Stage	Whole pelvic dose (Gy)	HDR fraction (LDR equiv. dose)	BED Gy_{10}[a]	LQED[b] (Gy)
I/II, nonbulky	45	6 Gy × 4 (32)	92	77
I/II, bulky	45	6 Gy × 5 (40)	102	85
III/IVA	50	6 Gy × 5 (40)	109	90

[a] Biologic effective dose (BED) = Total dose (relative effectiveness)
$= nd(1 + d/\alpha/\beta)$.

[b] Linear-quadratic effective dose for a 2-Gy fraction (LQED) = BED/relative effectiveness
$= \text{BED}/(1 + d/\alpha/\beta)$.

In the early 1990s, HDR implants were delivered on a once-weekly schedule after the completion of whole pelvis radiotherapy. This schedule was changed to twice weekly in the late 1990s because of prolonged treatment durations. Each patient's first HDR intracavitary insertion was performed in the operating room using the Fletcher–Williamson HDR applicator set under general or spinal anesthesia. Ultrasound guidance was used to improve visualization of the uterine cavity and prevent perforation. Subsequent implants were performed in the radiation oncology department using conscious sedation to keep the patient comfortable during the procedure. AP and lateral films were taken on our Ximatron (Varian Medical Systems, Palo Alto, CA) for treatment planning purposes. Our department uses the ^{192}Ir Nucletron MicroSelectron HDR unit (Nucletron B.V., Veenendaal, The Netherlands) and the associated Plato software (Nucletron) for treatment planning. This procedure was tolerated well by most patients; total time in the department was approximately 3 h. In the LDR group, our standard intracavitary brachytherapy was delivered in two implants. All implants were performed in the operating room under general or spinal anesthesia with ultrasound guidance using a Fletcher–Suit applicator. The prescribed dose to Point A for LDR patients was a minimum of 80–85 Gy, which includes the external pelvic radiation dose.

Chemotherapy

Chemotherapy was given to patients at the discretion of the treating radiation oncologist and gynecologic oncologist, or per protocol. Thirty-five percent of all patients received some type of chemotherapy. In the LDR group, 39% of patients received chemotherapy vs. 31% in the HDR group. The most commonly used drugs were cisplatin and hydrea. Routine concurrent chemoradiation started in 1999 using weekly cisplatin at 40 mg/m^2.

Statistics

The primary endpoints assessed in our review were locoregional control, disease-free survival, overall survival, and first site of failure. Endpoints were estimated using the Kaplan–Meier method and comparisons between treatment groups were performed using the log-rank test.

Results

The median followup was 48 months (ranging 2–104 months) for the LDR group and 59 months (ranging 0–136 months) for the HDR group ($p = 0.38$). Looking at the number of patients treated in each group over the total time period, there was a trend for more patients to receive HDR from 1996 to 2000 (34 patients) than from 1990 to 1995 (23 patients). The locoregional control and cause-specific survival at 3 years for the two groups are given in Table 3. Locoregional control was 76% for HDR and 78% for LDR ($p = 0.96$) (Fig. 1). For Stage IB1, locoregional control was 100% for both HDR and LDR. It was 87% for HDR vs. 90% ($p = 0.98$) for LDR in IB2 disease, 60% vs. 76% ($p = 0.38$) for Stage II, and 83% vs. 72% ($p = 0.96$) for Stage III, respectively. There was no statistical difference in disease-free survival ($p = 0.52$) or overall survival ($p = 0.48$) at 3 years for HDR (72% and 55%, respectively) compared to LDR (68% and 60%, respectively) (Fig. 2).

Thirty-five percent of patients received chemotherapy as part of their treatment regimen. Typically, weekly cisplatin or hydrea was used. When looking at the influence of chemotherapy, there was no statistical difference in outcome

Table 3
Clinical endpoints at 3 years comparing HDR to LDR brachytherapy for carcinoma of the cervix

LDR vs. HDR (# pts)	Locoregional control (%)		Cause-specific survival (%)	
Overall				
HDR (49)	76		59	
LDR (97)	78	$p = 0.96$	62	$p = 0.88$
Stage IB1				
HDR (5)	100		100	
LDR (3)	100		75	$p = 0.41$
Stage IB2				
HDR (19)	87		67	
LDR (12)	90	$p = 0.98$	62	$p = 0.75$
Stage II				
HDR (21)	60		57	
LDR (56)	76	$p = 0.38$	67	$p = 0.95$
Stage III				
HDR (6)	83		33	
LDR (23)	72	$p = 0.96$	45	$p = 0.48$

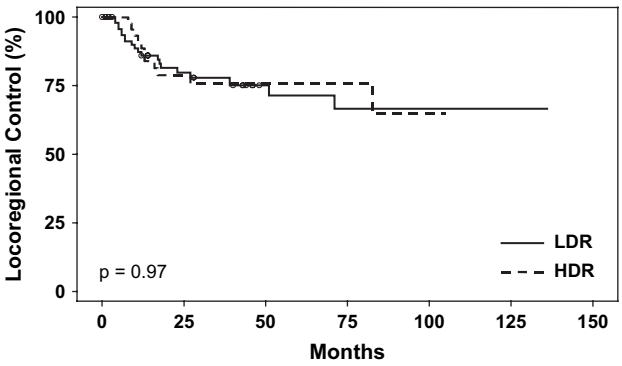

Fig. 1. Locoregional control by time.

between the patients who received chemotherapy and those who did not (Table 4). The cause-specific survival for HDR patients who received chemotherapy was 53.2% and 61.1% for those who did not get chemotherapy vs. 64.6% for LDR patients who received chemotherapy and 59.0% for those who did not get chemotherapy ($p = 0.42$). The overall survival for HDR with and without chemotherapy vs. LDR with and without chemotherapy was not statistically different ($p = 0.62$).

The median total treatment time was 66 days for HDR and 58 days for LDR patients. Overall duration of treatment effected a statistically significant trend for disease-free survival in both LDR ($p = 0.06$) and HDR ($p = 0.03$). During the time of this review, the majority of our patients were treated with only one HDR fraction per week after the completion of external beam therapy. Our current standard is two HDR fractions per week.

Of the 46 patients that failed, 56% had a locoregional recurrence as the first site of failure. Twenty-six percent of the patients failed distantly only, with 17% having both locoregional and distant disease as the first site of failure. Patients did not routinely undergo CT scans after treatment unless prompted by symptomatology.

Grade 1 or 2 toxicity was not well documented. Twelve patients had surgical intervention for either fistula or bowel obstruction during the followup period. Of those 12 patients, 4 (7%) were in the HDR group, and 8 (7.8%) in the LDR group. Two of the four in the HDR group had a pelvic recurrence associated with the fistula. The other two women were cancer free. In the LDR group, three women experienced a pelvic recurrence associated with their surgical intervention. Five women in the LDR group were free of disease. If we exclude the patients with a recurrence, because it is unclear in these patients if the cause of the toxicity was from the tumor or the treatment, then the Grade 3 toxicity rate is 3.5% (2/57) for HDR and 4.8% (5/103) for LDR.

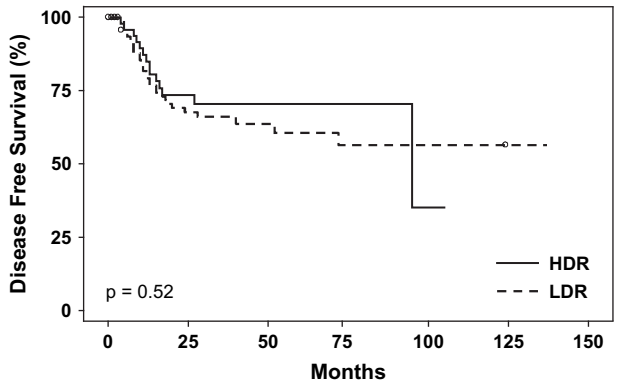

Fig. 2. Disease-free survival by time.

Table 4
Comparison of endpoints at 3 years with and without chemotherapy

HDR vs. LDR Chemo vs. no chemo	Cause-specific survival (%)	Overall survival (%)
No chemo/LDR	60	60
No chemo/HDR	61	56
Chemo/LDR	66	60
Chemo/HDR	57	54

Discussion

The primary concern of using HDR brachytherapy is a potential late toxicity due to large doses per fraction. This biologic disadvantage can be overcome through adequate fractionation and total dose. In the United States, when external beam radiotherapy and HDR brachytherapy are combined, the goal is to treat Point A to an LDR equivalent of 80 Gy for nonbulky disease and 85–90 Gy for bulky disease. The American Brachytherapy Society (ABS) developed guidelines for HDR brachytherapy, which are based on published literature and the linear-quadratic equation (15). A common HDR schedule used in the United States for advanced cervical cancer is 6 Gy × 5 fractions, in combination with 45 Gy to the whole pelvis. This schedule, which yields a biologic effective dose (BED) 101 Gy_{10}, is the current Radiation Therapy Oncology Group and Gynecologic Oncology Group standard. Current HDR fractionation schedule at UAB is similar to the ABS recommendation.

Our study shows that stage for stage the locoregional control, cause-specific survival, and overall survival are similar between HDR and LDR. Our study differed from other retrospective studies in several ways. First, both LDR and HDR groups were treated during same period (Table 5). Second, either HDR or LDR brachytherapy was offered to patients with respect to their preference. As a tertiary care center, many patients have been referred from outside our local area. As a result, most of these patients prefer to have LDR because of transportation concern. Furthermore, some patients prefer to have the lower number of brachytherapy associated with LDR. Third, patients with advanced tumor received median dose 45 Gy

Table 5
LDR and HDR brachytherapy by year

	1990–1991	1992–1993	1994–1995	1996–1997	1998–2000	Total
LDR	19 (63%)	14 (78%)	23 (74%)	14 (54%)	33 (60%)	103 (64%)
HDR	11 (37%)	4 (22%)	8 (26%)	12 (46%)	22 (40%)	57 (36%)
Total	30	18	31	26	55	160

to the whole pelvis before brachytherapy in both LDR and HDR groups.

The locoregional control rates of HDR and LDR groups are similar in both the UAB and the University of Wisconsin series except Stage IIIB disease. Both institutions prescribed similar total doses to Point A in HDR and LDR. They (16) reported that the 3-year actuarial pelvic control rate was inferior for IIIB disease when HDR brachytherapy was used instead of LDR (45% and 75%, respectively). Their first HDR brachytherapy was initiated as soon as possible, whereas our first HDR brachytherapy started after a higher dose of external radiotherapy was given to the whole pelvis. Therefore, they concluded that higher doses of external beam radiotherapy should be delivered before initiating brachytherapy to allow for adequate tumor regression. In our study, the 3-year actuarial local control rate for Stage IIIB disease was similar between LDR and HDR brachytherapy (72% and 83%, respectively). All of our Stage IIIB disease patients received whole pelvic external radiotherapy to median dose 45 Gy before the first intracavitary insertion. Dulcos *et al.* (17) also reported that the timing of HDR brachytherapy showed a significant impact on local control for Stage IIIB disease (87% vs. 46% [$p = 0.02$]) in favor of those delayed in HDR brachytherapy until a higher external beam dose was delivered. Chao *et al.* (18) indicated that the early use of a midline block in the high-dose brachytherapy region might increase the risk of paracentral recurrences, particularly for patients with uterosacral involvement.

Our cause-specific survival and overall survival are comparable to those of other institutions (11, 12, 14). Variations of survivals in different institutions could be due to the difference in patient population of tumor volume and comorbidity between the institutions.

Some studies show that overall treatment time is an important prognostic factor in both LDR (19–21) and HDR (22) brachytherapy. Our study showed that overall duration of treatment affected a significant trend for disease-free survival in both LDR and HDR. Therefore, it is imperative to optimize the treatment strategy by shortening treatment duration. During this review period, most HDR fractionation was delivered once weekly. This prolonged the overall treatment time to a median of 66 days for HDR compared to 58 days for LDR. Because the delay of HDR until the end of external beam treatment can prolong total treatment time, our institution now routinely performs two HDR fractions per week. Hama *et al.* (23) have reported that patients treated with a twice-weekly HDR brachytherapy schedule had better rates of local control without a higher incidence of late Grades 2–3 complications when compared to patients treated with once-weekly treatment.

Results comparing the incidence of late complications between LDR and HDR brachytherapy are conflicting (11, 24, 25). Because of wide variations of the scoring system and the high subjectivity of late complications, it is difficult to compare different clinical studies. Several investigators have analyzed the probability of late complications as a function of total BED at International Commission on Radiation Units and Measurements (ICRU) 38 reference points. They indicated that a threshold for severe rectal complications was BED 110–125 Gy_3 (24, 26, 27). Recently, a number of investigators explored CT-based three-dimensional (3-D) treatment planning to compare with the ICRU reference bladder and rectal point doses. These studies demonstrated that the maximum bladder and rectal volume doses generated from dose–volume histograms were 1.28–2.5 and 0.92–1.93 times greater than ICRU reference bladder and rectal point doses, respectively (28–30).

In our study, concurrent chemotherapy did not affect outcome in our patients, possibly because of patient selection, small patient numbers, and the specific type of chemotherapy used. In this study, a small number of patients were treated with concurrent chemoradiotherapy since the routine use of concurrent chemoradiotherapy started in 1999. Information regarding concurrent chemoradiotherapy with HDR brachytherapy is scarce in the literature because most experience of combination chemotherapy and radiotherapy was based on LDR brachytherapy. However, the ABS recommended that chemotherapy should not be administered concomitantly with HDR brachytherapy unless it is the context of controlled clinical trials (15). The current treatment policy at UAB is to use concurrent chemoradiotherapy for advanced cervical cancer in both LDR and HDR brachytherapy during the external beam portion of therapy.

HDR brachytherapy fractionation schedules reported in the literature vary markedly (6, 31, 32). Petereit and Pearcey (33) performed a literature analysis to evaluate if doses could correlate with local control for each stage of cervical cancer. However, a dose–response relationship could not be identified for either tumor or late tissue complications. They were surprised to find that excellent results were reported with low-dose schedules in studies by Toita *et al.* (34) (6 Gy × 3), Ogino *et al.* (24) (6 Gy × 4), Pearcey *et al.* (35) (8 Gy × 3), and Sood *et al.* (36) (9 Gy × 2), in combination with 45 Gy to the whole pelvis. This was

particularly evident in the Japanese literature. These findings do not necessarily question the validity of the linear-quadratic model. Recently, Toita *et al.* (34) postulated that after 40 Gy of external beam radiation, significant tumor regression would place the disease within the high-dose gradient and thus render these lower doses tumoricidal.

The importance of tumor volume as a predictor of prognosis in patients with cancer of the cervix is well documented (37–41). Our previous study (42) shows that tumor size varies widely within each stage and overlaps between stages. Also, another one of our studies (43) and others (44, 45) show that there is significant tumor shrinkage after whole pelvic radiotherapy before intracavitary brachytherapy. This tumor shrinkage is usually rapid and occurs within a few weeks. Therefore, tumor size just before brachytherapy is of more prognostic significance than original tumor size for local control and overall survival (46, 47). Without tumor size data, meaningful comparison of the dose–response relationship for local control and survival is difficult.

Several authors (48–50) demonstrated that unfavorable tumor coverage by prescription to Point A was one of the reasons for the poor local control in patients with larger tumor volume. To evaluate the dose–response relationship, image-based 3-D treatment planning is a better method than conventional radiography-based treatment planning. In the current era of modern medical imaging technology and computer software, attempts have been made to evaluate the tumor dose by image-based 3-D treatment planning (29, 51, 52).

Conclusion

Our study confirmed equivalence in pelvic control, cause-specific survival, and overall survival as well as late morbidity between LDR and HDR brachytherapy. When advanced disease is treated with either LDR or HDR brachytherapy, higher whole pelvic external doses are beneficial to shrink the tumor before intracavitary brachytherapy. To evaluate the dose–response relationship for HDR and LDR brachytherapy, it is necessary to explore image-based 3-D treatment planning for cancer of the cervix.

References

[1] Cleaves MA. Radium therapy. *Chic Med Rec* 1903;64:601.
[2] Beth E, Eifel P, Moughan J, *et al*. Patterns of brachytherapy practice for patients with carcinoma of the cervix (1966–1999): A Patterns of Care Study. *Int J Radiat Oncol Biol Phys* 2005;63:1083–1092.
[3] Henschke UK, Hilaris BS, Mahan DG. Remote afterloading with intracavitary applicators. *Radiology* 1964;83:344–345.
[4] O'Connell D, Howard N, Joslin CA, *et al*. A new remotely controlled unit for the treatment of uterine cancer. *Lancet* 1965;18:570–571.
[5] Joslin CA, Smith CW, Mallik A. The treatment of cervix cancer using high activity Cobalt^{60} sources. *Br J Radiol* 1972;45:257–270.
[6] Fu KK, Phillips TL. High-dose-rate versus low-dose-rate intracavitary brachytherapy for carcinoma of the cervix. [see comments]. *Int J Radiat Oncol Biol Phys* 1990;19:791–796.
[7] Cikaric S. Radiation therapy of cervical carcinoma using either HDR or LDR afterloading: Comparison of 5-year results and complications. *Strahlenther Onkol* 1988;82:119–122.
[8] Shigematsu Y, Nishiyama K, Masaki N, *et al*. Treatment of carcinoma of the uterine cervix by remotely controlled afterloading intracavitary radiotherapy with high-dose rate: A comparative study with a low-dose-rate system. *Int J Radiat Oncol Biol Phys* 1983;9: 351–356.
[9] Inoue T, Hori S, Miyata Y, *et al*. High versus low dose rate intracavitary irradiation of carcinoma of the uterine cervix—A preliminary report. *Acta Radiol Oncol* 1978;17:277–282.
[10] Kucera H, Potter R, Knocke TH, *et al*. High-dose versus low-dose rate brachytherapy in definitive radiotherapy of cervical cancer. *Wien Klin Wochenschr* 2001;113:58–62.
[11] Teshima T, Inoue T, Ikeda H, *et al*. High-dose rate and low-dose rate intracavitary therapy for carcinoma of the uterine cervix. Final results of Osaka University Hospital. *Cancer* 1993;72:2409–2414.
[12] Patel FD, Sharma SC, Negi PS, *et al*. Low dose rate vs. high dose rate brachytherapy in the treatment of carcinoma of the uterine cervix: A clinical trial. *Int J Radiat Oncol Biol Phys* 1994;28: 335–341.
[13] Hareyama M, Sakata K, Oouchi A, *et al*. High-dose-rate versus low-dose-rate intracavitary therapy for carcinoma of the uterine cervix: A randomized trial. *Cancer* 2002;94:117–124.
[14] Lertsanguansinchai P, Lertbutasayanukul C, Shotelersuk K, *et al*. Phase III randomized trial comparing LDR and HDR brachytherapy in treatment of cervical carcinoma. *Int J Radiat Oncol Biol Phys* 2004;59:1424–1431.
[15] Nag S, Erickson B, Thomadsen B, *et al*. For the American Brachytherapy Society. The American Brachytherapy Society recommendations for high-dose-rate brachytherapy for carcinoma of the cervix. *Int J Radiat Oncol Biol Phys* 2000;48:201–211.
[16] Petereit DG, Sardaria JN, Potter DM, *et al*. High-dose-rate versus low-dose-rate brachytherapy in the treatment of cervical cancer analysis of tumor recurrence—The University of Wisconsin. *Int J Radiat Oncol Biol Phys* 1999;45:1267–1274.
[17] Dulcos M, Souhami L, Corns R, *et al*. Cervical cancer: Timing of high-dose rate brachytherapy with external beam radiotherapy. *Radiother Oncol* 2001;58:514.
[18] Chao KSC, Williamson JF, Grigsby PW, *et al*. Uterosacral space involvement in locally advanced carcinoma of the uterine cervix. *Int J Radiat Oncol Biol Phys* 1998;40:397–403.
[19] Larciano RM, Pajak TF, Martz K, *et al*. The influence of treatment time on outcome for squamous cell cancer of the uterine cervix treated with radiation: A Patterns-of-Care study. *Int J Radiat Oncol Biol Phys* 1993;25:391–398.
[20] Fyles A, Kene TJ, Barton M, *et al*. The effect of treatment in the local control of cervix cancer. *Radiother Oncol* 1992;25:273–279.
[21] Perez CA, Grigsby PW, Castro-Vita H, *et al*. Carcinoma of the uterine cervix. Impact of prolongation of overall treatment time and timing of brachytherapy on outcome of radiation therapy. *Int J Radiat Oncol Biol Phys* 1995;32:1275–1288.
[22] Chen S, Liang J, Yang S, *et al*. The adverse effect of treatment prolongation in cervical cancer by high-dose-rate intracavitary brachytherapy. *Radiother Oncol* 2003;67:69–76.
[23] Hama Y, Uematsu M, Nagata I, *et al*. Carcinoma of the uterine cervix: Twice- versus once-weekly high-dose-rate brachytherapy. *Radiology* 2001;219:207–212.
[24] Ogino I, Kitamura T, Okamoto N, *et al*. Late rectal complication following high dose rate intracavitary brachytherapy in cancer of the cervix. *Int J Radiat Oncol Biol Phys* 1995;31:725–734.
[25] Ferrigno R, Novaes PERDS, Pellizzon ACA, *et al*. High-dose-rate brachytherapy in the treatment of uterine cervix cancer. Analysis of dose effectiveness and late complications. *Int J Radiat Oncol Biol Phys* 2001;50:1123–1135.
[26] Clark BG, Souhami L, Roman TN, *et al*. The prediction of late rectal complications in patients treated with high dose-rate brachytherapy

for carcinoma of the cervix. *Int J Radiat Oncol Biol Phys* 1997;38: 989–993.

[27] Chen MS, Lin FJ, Hong CH, *et al*. High-dose-rate afterloading technique in the radiation treatment of uterine cervical cancer: 399 cases and 9 years experience in Taiwan. *Int J Radiat Oncol Biol Phys* 1991; 20:915–919.

[28] Schoeppel SL, LaVigne ML, Martel MK, *et al*. Three-dimensional treatment planning of intracavitary gynecologic implants: Analysis of ten cases and implication for dose specification. *Int J Radiat Oncol Biol Phys* 1994;28:277–283.

[29] Briot E, Crevoisier D, Petrow P, *et al*. Dose–volume histogram analysis for tumor and critical organs in intracavitary brachytherapy of cervical cancer with the use of MRI. (Abstr.). *Radiother Oncol* 2001; 60:S3.

[30] Fellner C, Potter R, Knocke TH, *et al*. Comparison of radiography- and computed tomography-based treatment planning in cervix cancer in brachytherapy with special attention to some quality assurance aspects. *Radiother Oncol* 2001;58:53–62.

[31] Okawa I, Sakata S, Kita-Okawa M. Comparison of HDR versus LDR regimens for intracavitary brachytherapy of cervical cancer: Japanese experience. In: Mould RF, editor. *International brachytherapy.* Veenendaal, The Netherlands: Nucletron B.V.; 1992. p. 13–17.

[32] Orton CG, Seyedsadr M, Somnay A. Comparisons of high and low dose rate remote afterloading for cervix cancer and the importance of fractionation. *Int J Radiat Oncol Biol Phys* 1991;21:1425–1434.

[33] Petereit DG, Pearcey R. Literature analysis of high dose rate brachytherapy fractionation schedules in the treatment of cervical cancer: Is there an optimal fractionation schedule? *Int J Radiat Oncol Biol Phys* 1999;43:359–366.

[34] Toita T, Kakinohana Y, Ogawa K, *et al*. Combination external beam radiotherapy and high-dose-rate intracavitary brachytherapy for uterine cervical cancer: Analysis of dose and fractionation schedule. *Int J Radiat Oncol Biol Phys* 2003;56:1344–1353.

[35] Pearcey R, Brundage M, Drouin P, *et al*. Phase III trial comparing radical radiotherapy with, and without cisplatin chemotherapy in patients with advanced squamous cell cancer of the cervix. *J Clin Oncol* 2002;20:966–972.

[36] Sood B, Gorla G, Grupta S, *et al*. Two fractions of high-dose rate brachytherapy in the management of cervix cancer: Clinical experience with and without chemotherapy. *Int J Radiat Oncol Biol Phys* 2002; 53:702–706.

[37] Barrillot I, Horiot JC, Pegneaux J, *et al*. Carcinoma of the intact uterine cervix treated with radiotherapy alone: French cooperative study: Update and multi-variate analysis of prognostic factor. *Int J Radiat Oncol Biol Phys* 1997;38:969–978.

[38] Eifel PJ, Morris M, Wharton JT, *et al*. The influence of tumor size and morphology on the outcome of patients with FIGO stage IB squamous cell carcinoma of the uterine cervix. *Int J Radiat Oncol Biol Phys* 1994;29:9–16.

[39] Perez CA, Grigsby PW, Nene SM, *et al*. Effect of tumor size on the prognosis of carcinoma of the uterine cervix treated with irradiation alone. *Cancer* 1992;69:2796–2806.

[40] Hsu HC, Leung SW, Huang EY, *et al*. Impact of the extent of parametrial involvement in patients with carcinoma of the uterine cervix. *Int J Radiat Oncol Biol Phys* 1998;40:405–410.

[41] Ito H, Kutuki S, Nishiguchi I, *et al*. Radiotherapy for cervical cancer with high-dose rate brachytherapy—Correlation between tumor size and failure. *Radiother Oncol* 1994;31:240–247.

[42] Kim RY, Caranto JF, Tucker JC. Image-based intracavitary brachytherapy in cancer of the cervix: Analysis of CT-based tumor coverage by pear-shaped isodose dimensions. (Abstr.). *Int J Radiat Oncol Biol Phys* 1997;39:299.

[43] Kim RY, Spencer SA. Tumor shrinkage before intracavitary brachytherapy for cancer of the cervix: Radiotherapy alone versus concurrent chemo-radiotherapy. *Cancer J* 2000;6:377–380.

[44] Lee CM, Shrieve DC, Gaffney DK. Rapid involution and mobility of carcinoma of the cervix. *Int J Radiat Oncol Biol Phys* 2004;58: 625–630.

[45] Dinniwell R, Chan P, Milosevic M, *et al*. Assessment of radiotherapy response using magnetic resonance imaging tumor volumetry in carcinoma of the uterine cervix. *Radiat Oncol* 2004;72:S58.

[46] Hong JH, Chen MS, Lin FJ, *et al*. Prognostic assessment of tumor regression after external irradiation for cervical cancer. *Int J Radiat Oncol Biol Phys* 1992;22:913–917.

[47] Mayr NA, Yuh W, Zheng J, *et al*. Tumor size evaluated by pelvic examination compared with 3-D MR quantitative analysis in the prediction of outcome for cervical cancer. *Int J Radiat Oncol Biol Phys* 1997;39:395–404.

[48] Mizoe J. Analysis of the dose–volume histogram in uterine cervical cancer of diagnostic CT. *Strahlenther Onkol* 1990;166:279–284.

[49] Terahara A, Nakano T, Ischikawa A, *et al*. Dose–volume histogram analysis of high dose rate intracavitary brachytherapy for uterine cervix cancer. *Int J Radiat Oncol Biol Phys* 1996;35:549–554.

[50] Suyama S, Nakaguchi T, Kawakami K, *et al*. Computed tomography analysis of causes of local failure in radiotherapy for cervical carcinoma. *Cancer* 1998;83:1956–1965.

[51] Gerstner N, Wachter S, Reinstadler E, *et al*. Radiography compared to sectional image (CT/MR) based 3D treatment planning in cervix cancer brachytherapy: Results of a perspective comparative trial. (Abstr.). *Radiother Oncol* 2001;60:S3.

[52] Kim RY, Pareek P. Radiography-based treatment planning compared with computed tomography (CT)-based treatment planning for intracavitary brachytherapy in cancer of the cervix: Analysis of dose–volume histograms. *Brachytherapy* 2003;2:200–206.