

RAPID INVOLUTION AND MOBILITY OF CARCINOMA OF THE CERVIX

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Purpose: To quantitatively describe the involution and mobility of carcinoma of the cervix while under treatment with chemoradiotherapy (both with external beam radiation [EBRT] and high-dose-rate [HDR] intracavitary therapy). These data have implications for conformal or intensity modulated radiation therapy boost to the cervix.

Methods and Materials: Seventeen patients underwent HDR brachytherapy boost to the cervix and were evaluated by repeat clinical examinations. In most cases, 5 weekly HDR brachytherapy insertions were performed after approximately 2 to 3 weeks of the initiation of EBRT. Sequential clinical tumor sizes were recorded in the chart for each patient under treatment. Linear regression analyses were performed to analyze tumor size as a function of total dose of external beam plus brachytherapy and number of elapsed days during the treatment course. In addition, the mobility of the cervix was documented by placement of a uterine sleeve for HDR brachytherapy before the initiation of therapy, and changes in sleeve position were identified on portal films relative to the midline of the pubic symphysis, in three dimensions. The anatomic position of the cervix was also identified at the time of simulation for HDR brachytherapy.

Results: Seventeen patients were identified and selected to receive HDR brachytherapy at our institution. Sixteen of the 17 patients received concurrent chemotherapy. The median dose at which tumor was no longer clinically evident was 61.5 Gy (95% confidence interval [CI]: 50.7–72.3 Gy) by linear regression analysis. This indicates that the median dose to achieve a 50% reduction in tumor size is approximately 30.8 Gy. Similarly, the median number of elapsed days for a complete response was 42 days (95% CI: 34–50 elapsed days). This indicates that it takes 21 days to achieve a 50% clinical complete response for patients undergoing concurrent cisplatin-based chemoradiotherapy and HDR brachytherapy. In addition, the mobility of the cervix during EBRT was noted by serial measurements of the location of a metallic ring in the uterine sleeve, as seen on port films. The median and maximum ranges for change in the position of the cervix in the lateral (*x*), superior/inferior (*y*), and anterior/posterior (*z*) planes were 10, 8, and 16 mm and 24, 36, and 23 mm, respectively. Also, 85 brachytherapy procedures were performed, and the positions of the cervix on 170 orthogonal films were evaluated. The median and maximum ranges for the position of the cervix at the time of HDR brachytherapy in the lateral (*x*), superior/inferior (*y*), and anterior/posterior (*z*) planes were 5, 12, and 10 mm and 11, 25, and 32 mm, respectively.

Conclusions: Carcinoma of the cervix involutes rapidly with EBRT, concurrent cisplatin-based chemotherapy, and HDR brachytherapy. The time for 50% tumor regression was calculated to be 21 days and occurs after 30.8 Gy. In addition, uterine sleeve placement allowed us to document the median and maximum ranges of cervical mobility during the treatment course of EBRT to be 8–16 mm and 23–36 mm, and at the time of HDR brachytherapy to be 5–12 mm and 11–32 mm, respectively. These data indicate that the cervix gross tumor volume changes rapidly in a systematic fashion during chemoradiotherapy and, together with the mobility of the cervix, urge caution in nonbrachytherapy boost planning. © 2004 Elsevier Inc.

Cervix cancer, Radiation therapy, IMRT, Mobility, Shrinkage.

INTRODUCTION

Treatment of locally advanced cervical cancer requires the judicious use of external beam radiotherapy (EBRT) and brachytherapy for optimal results. In February 1999, a clinical alert was published by the National Cancer Institute of the United States, indicating the superiority of cisplatin-based chemoradiotherapy compared to radiotherapy alone

(1, 2). Eifel has suggested that the addition of chemotherapy was the first significant advance in the management of carcinoma of the cervix in 40 years (3). The addition of chemotherapy to radical radiation therapy has clearly increased toxicity. In RTOG 9001, only two-thirds of patients on the chemoradiotherapy arm received all three cycles of 5-fluorouracil and cisplatin (1).

It is possible that three-dimensional conformal treat-

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Table 1. Patient characteristics

Patient	Age (years)	FIGO stage	Initial tumor size (cm)	Total dose (Gy)	Brachytherapy dose (Gy)	Histology	Follow-up (months)	Disease status	Site of recurrence
1	42	IIIB	10	75.8	30	SCCA	14	NED	
2	26	IIB	10	84	36	SCCA	4	NED	
3	60	IIB	5.5	75	30	SCCA	21	R	Lung
4	81	IIA	2	75	30	SCCA	9	R	Lung/Liver
5	46	IVA	7	75	30	SCCA	0	PR	Cervix
6	57	IIB	6	71.1	25.5	SCCA	1	NED	
7	39	IIIB	10	75	30	SCCA	14	NED	
8	60	IIB	5.5	75	30	SCCA	11	NED	
9	59	IIB	7	75	30	Adeno	9	NED	
10	40	IIB	7	75	30	SCCA	35	NED	
11	47	IIB	7	81.9	31.5	SCCA	4	R	Supraclavicular
12	57	IIB	6	82.2	30	SCCA	6	NED	
13	45	IB	3.5	75	30	SCCA	8	NED	
14	61	IIB	6	70.5	25.5	SCCA	1	NED	
15	58	IIB	4	75	30	SCCA	3	NED	
16	69	IIIB	8	84	30	SCCA	3	NED	
17	58	IIB	4.5	75	30	SCCA	16	NED	
Median	57		6	75	30		8		
Range	26–81		2–10	70–84	25–36		0–35		

Abbreviations: Adeno = adenocarcinoma; NED = no evidence of disease; PR = partial response only; R = recurrent disease; SCCA = squamous cell carcinoma.

ment (3D-CRT) planning or intensity-modulated radiation therapy (IMRT) may also be a significant advance in the management of patients with advanced cervical cancer (4–8). Some studies have already documented a reduction in organ-specific toxicity with the utilization of IMRT in treatment of cervix cancer (8, 9). IMRT and 3D-CRT depend upon the ability to identify and analyze volumes of interest from diagnostic studies such as CT and MRI (10–13). These methods deliver radiation doses and dose distributions that have been shown to better conform to the tumor and minimize direct irradiation of surrounding critical organs (14–16). With the use of modern imaging techniques, radiation oncologists are able to delineate and contour structures of interest with a high degree of accuracy. In some cases, volumes of interest can be accurately defined to within 1 millimeter (12).

The effective use of 3D-CRT requires reproducible patient positioning, accurate tumor delineation, and freedom from organ motion, or methods to compensate for motion. Additionally, tumor response or shrinkage may cause sizeable volumes of normal tissue or organs at risk to “fall into” the planning target volume (PTV). Tumor mobility and shrinkage may cause a geographic miss for 3D-CRT/IMRT-based boost plans; alternatively, organs at risk may be overdosed inadvertently. This study evaluates changes in position and volume of the cervix during the course of both external beam and high-dose-rate (HDR) brachytherapy.

The present study approaches the problem of target motion through analysis of serial portal films taken before initiation of treatment and during treatment with radiation therapy. The positional differences observed between portal films were taken as representative of target motion that

occurs between image acquisition, treatment planning, and treatment delivery. Because target volume shrinkage can be a significant factor in cervix cancer treatment, assessments of changes in target volume during treatment were also included in our analysis.

METHODS AND MATERIALS

Radiation therapy medical records and portal films were reviewed for 17 patients with carcinoma of the cervix treated at the University of Utah Health Sciences Center. These patients were diagnosed with locally advanced cervical cancer and were selected to receive HDR brachytherapy boost to the cervix along with EBRT. In general, patients received 5 weekly HDR brachytherapy insertions after approximately 2 to 3 weeks after the initiation of EBRT. Clinical tumor size was determined during EBRT by way of a standard bimanual examination with the patient in the dorsal lithotomy position. At the time of each brachytherapy procedure, a clinical tumor size was recorded during examinations under anesthesia before placement of modified Fletcher-Suit HDR tandem and ovoid devices.

Patients received the external beam component of their treatments with 6, 10, or 18 MV photons in once-daily fractions of 1.8 Gy and received 5 treatments per week. Patient characteristics are listed in Table 1. All 17 patients were identified and selected to receive HDR brachytherapy, and intracavitary HDR implants were performed with modified Fletcher-Suit applicators. Sixteen of the 17 patients received concurrent cisplatin-based chemotherapy.

In addition, for HDR brachytherapy, a uterine sleeve

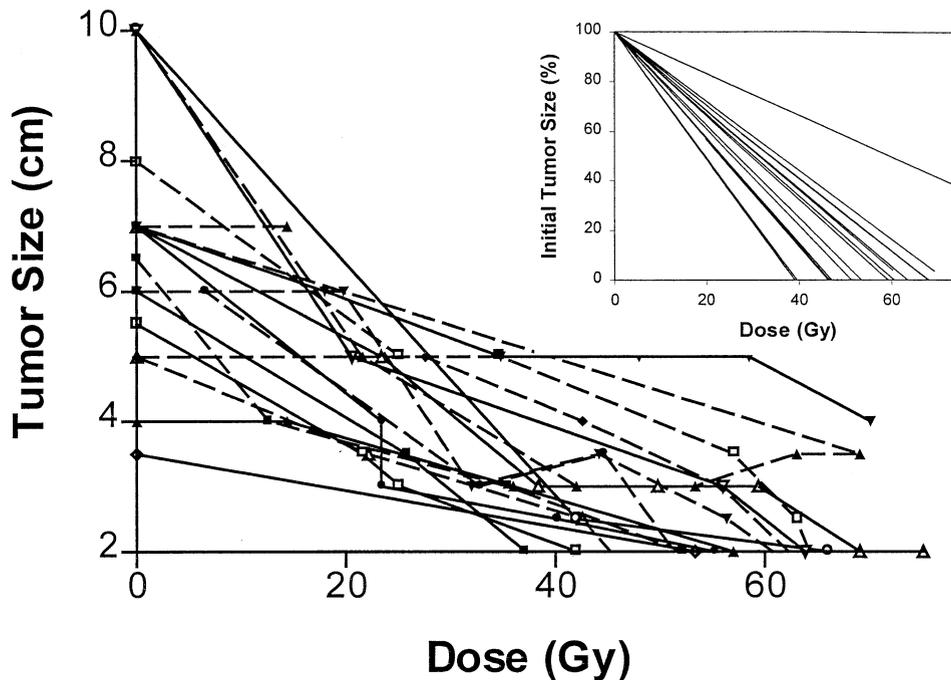


Fig. 1. Tumor size as a function of total dose (external beam plus brachytherapy) for 17 patients. Inset shows the initial tumor size normalized to 100%. Linear regression analyses were performed to determine the rapidity of response.

with a metallic ring at the location of the cervix was sutured in place for 15 of 17 patients before the initiation of therapy. Because of the radiopacity of the metallic ring, changes in sleeve position/cervix location were measured in reference to the midline of the pubic symphysis on weekly port films. All port films of the 15 patients who had sleeves placed were examined, and the position of the cervical marker could be identified on 65 films from 11 patients. The location of the uterine sleeve was systematically measured in each of the weekly anteroposterior and lateral port films with the midline of the pubic symphysis as reference. Variation in cervix position was determined in three dimensions. Identical measurements were performed to assess the mobility of the cervix at the time of HDR brachytherapy through analysis of orthogonal simulation films. Eighty-five implants were performed on the 17 patients (average: 5 per patient), and thus, 85 pairs of orthogonal simulation films were reviewed.

To evaluate response to treatment, serial measurements of cervix diameter for each patient were obtained before initiation of treatment and throughout treatment with both external beam and intracavitary radiation therapy. The initial measurements of cervix diameter were normalized to 100%. In addition, a normal cervix was determined to be 2 cm in diameter, and consequently, 2 cm was subtracted from the initial pretreatment cervix diameter before normalization for comparison between patients. Linear regression analyses were performed to analyze tumor size as a function of total dose of external beam plus brachytherapy and as a function of number of elapsed days through the treatment course. These patients

have been followed for an average of 10 months (range: 1–35 months) after completion of therapy.

RESULTS

Patient characteristics are listed in Table 1. The population studied had a median age of 57 years (range: 26–81 years) at time of diagnosis. The median tumor size was 6 cm (range: 2–10 cm) at time of diagnosis. Sixteen patients had a histologic diagnosis of squamous cell carcinoma, and 1 patient was diagnosed with adenocarcinoma. The median total radiation dose was 7500 cGy (range: 7050–8400 cGy). The brachytherapy component of treatment was prescribed to an average dose of 3000 cGy (range: 2550–3600 cGy). Sixteen of the 17 patients received concurrent chemotherapy, and all patients except 1 have been locally controlled with a median follow-up of only 10 months. At time of analysis, 13 of 17 patients had no evidence of disease recurrence.

Figures 1 and 2 illustrate the change in tumor size with respect to radiation dose and number of elapsed days of treatment, respectively. Linear regression analyses were then performed for each patient data set. On the insets of Figs. 1 and 2 are shown, respectively, percent initial tumor size as a function of total radiation dose and number of elapsed days of treatment. The median dose at which the tumor was no longer clinically evident was 61.5 Gy (95% CI: 50.7–72.3 Gy) by linear regression analysis. This indicates that the median dose to achieve a 50% reduction in tumor size is approximately 30.8 Gy. Similarly, the median number of elapsed days for a complete response was 42

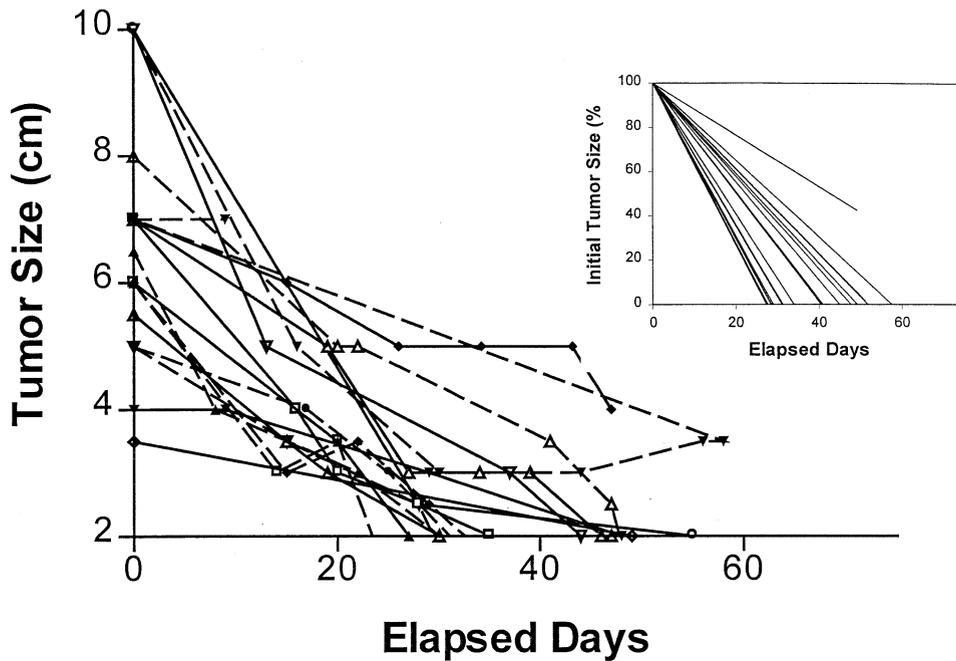


Fig. 2. Tumor size as a function of number of elapsed treatment days (external beam plus brachytherapy) for 17 patients. Inset shows the initial tumor size normalized to 100%. Linear regression analyses were performed to determine the rapidity of response.

days (95% CI: 34–50 elapsed days); consequently, the median number of elapsed days to achieve a 50% reduction in tumor size was 21 days.

In addition, the mobility of the cervix during EBRT was measured by evaluation of the cervical marker on serial port films. The median change in position of the cervix in the lateral (x), superior/inferior (y), and anterior/posterior (z) planes was 10, 8, and 16 mm, respectively. The maximum

change in position of the cervix in the lateral (x), superior/inferior (y), and anterior/posterior (z) planes was 24, 36, and 23 mm, respectively (See Fig. 3).

In addition, 85 brachytherapy procedures were performed on the patients, and the positions of the cervix on 170 orthogonal films were evaluated. The median change in position of the cervix at the time of HDR brachytherapy in the lateral (x), superior/inferior (y), and anterior/posterior (z)

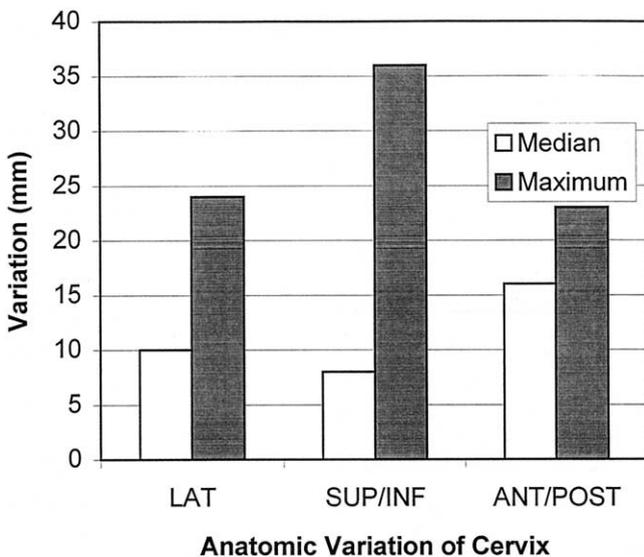


Fig. 3. Variation in position of the cervix during external beam treatments. Data shown are the median and maximum changes in position as seen on 65 portal films from 11 patients.

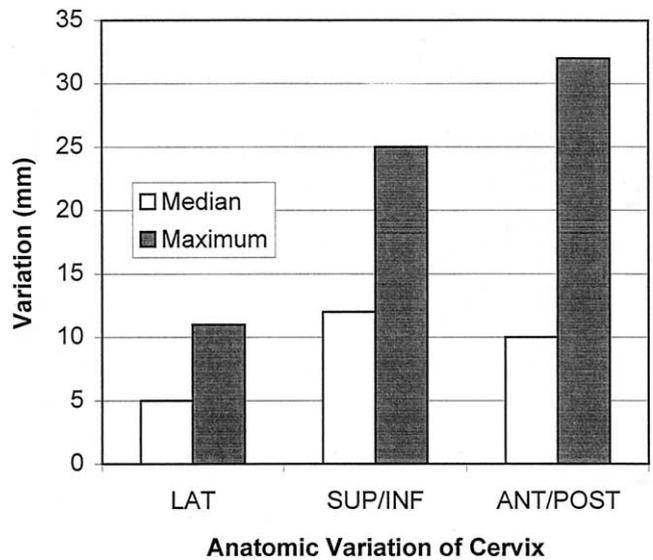


Fig. 4. Variation in position of the cervix during HDR brachytherapy. Data shown are the median and maximum changes in position as seen on 170 simulation films from 85 implant procedures on 17 patients.

planes was 5, 12, and 10 mm, respectively. The maximum change in position of the cervix at the time of HDR brachytherapy in the lateral (*x*), superior/inferior (*y*), and anterior/posterior (*z*) planes was 11, 25, and 32 mm, respectively (See Fig. 4).

DISCUSSION AND CONCLUSIONS

Although 3D-CRT and IMRT have the potential of improving tumor control with fewer normal-tissue complications, these techniques are particularly susceptible to treatment uncertainties such as variation in patient position, organ motion, and reduction in tumor volume. These modalities typically are designed with the assumption that all volumes defined by the imaging study remain rigidly fixed and remain unchanged throughout the course of image acquisition, treatment planning, and treatment delivery. Use of rigid patient immobilization devices in conjunction with laser-tattoo alignment to restrict variation in patient position is necessary. These techniques are also not exempt from error due to both skin mobility and patient body changes, such as weight loss during therapy (16, 17).

Studies of IMRT in gynecologic patients have described dosimetric benefits in terms of dose reduction to small bowel, bladder, rectum, and pelvic bone marrow (6–9). Decreasing normal-tissue toxicity by IMRT may permit a decrease in the total treatment time by permitting a higher fractional daily dose to the tumor compared to the pelvis, as elegantly reviewed by Kavanagh *et al.* (6). Reduction in organ-specific toxicity may also permit more aggressive use of systemic therapies.

There are limited published data describing internal organ motion within the pelvis of patients under treatment for cancer of the cervix, and no published analyses provide quantitative estimates of average systematic errors in target identifications for gynecologic structures while under chemoradiation therapy. Buchali *et al.* provide an analysis of 29 women with cervical or endometrial cancers, but the focus of the study was to describe the effect of bladder filling on pelvic viscera (18). The authors concluded that because of the mobility of the uterus, increased margins between the clinical target volume (CTV) and PTV superiorly, inferiorly, and anteriorly/posteriorly should be 15, 6, and 9 mm, respectively. They also described motion of the cervix to be 4 mm in the cranial/caudal direction (18). Kim *et al.* described the geometric variations of colpostat and tandem placement between high-dose-rate brachytherapy applications for cervical cancer. No consistent pattern of variation was found, except in vaginal packing (19). Bahena *et al.* also analyzed applicator positional reproducibility through interfraction positional variation. The translational variation of applicator position for all patients was determined to be 6.5 mm (superior to inferior), 5.9 mm (right to left), and 7.7 mm (anterior to posterior) (20). These data are similar to our findings that the median change in position of the cervix at the time of HDR brachytherapy in the lateral (*x*), superior/

inferior (*y*), and anterior/posterior (*z*) planes was 5, 12, and 10 mm, respectively.

Positional variation at the time of brachytherapy can be different from variation while under treatment with external beam radiation. We found a greater median deviation in cervix position during external beam treatments. Data collected in our study during external beam radiation indicate that to cover the cervix adequately, in 95% of cases, the increased margin between the CTV and PTV superiorly/inferiorly, laterally, and anteriorly/posteriorly should be 15.4 mm, 17.5 mm, and 22.9 mm, respectively. In addition, Christensen *et al.* reported that the large deformations of pelvic organs during external beam and brachytherapy could be modeled such that accurate cumulative dose distributions could be achieved (21). In this study, we observed that the median changes of cervical position in three dimensions during external beam therapy ranged from 8 to 16 mm; however, the maximal changes ranged from 23 to 36 mm. Recently, the use of portal imaging and adaptive radiotherapy to optimize dose level, improve the quality of dose delivery, and increase the applicability of IMRT has been described. These adaptive applications allow optimization of each patient's treatment according to specific anatomic information obtained during the course of treatment (22, 23). Thus, portal imaging and adaptive radiotherapy may be helpful future clinical tools to aid in avoidance of geographic miss.

The rapid and consistent reduction in the cervix gross tumor volume in this study indicates that it would not be prudent to image the patient before the initiation of external beam therapy and 4–6 weeks later employ those images for boost planning. As has been previously described, organ deformation can occur in a nonrandom fashion, and mathematical algorithms can be used to describe these changes (24). That is, in some cases, the CTV may need to be expanded in a nonuniform fashion to provide the best coverage of the PTV and to allow sparing of normal tissues.

The use of IMRT in locally advanced cervix cancer seems promising in reducing toxicity associated with radiation (6–9). However, it is uncertain whether IMRT could be used in place of brachytherapy. In part, brachytherapy for cervical carcinoma obviates the concerns regarding positional uncertainty, because the sources are in close proximity to the cervix. Additionally, the high dose gradients observed in intracavitary brachytherapy may be advantageous, because the cervical mucosa routinely is treated to doses of >10,000 cGy. It is likely that IMRT will complement brachytherapy in the definitive management of patients with advanced pelvic tumors.

These data indicate that carcinoma of the cervix involutes rapidly with EBRT, high-dose-rate brachytherapy, and concurrent cisplatin-based chemotherapy. The time required for 50% tumor regression was approximately 21 elapsed days, and after a dose of 30.8 Gy. In addition, uterine sleeve placement allowed us to document the median and maximum ranges for change in the position of the cervix during

EBRT at 8–16 mm and 23–36 mm, respectively, and at the time of HDR brachytherapy at 5–12 mm and 11–32 mm, respectively. These data urge caution in nonbrachytherapy

boost planning for the cervix, because of cervical mobility and the rapid involution of tumor, and suggest the necessity of portal imaging for this application.

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